

Clinical Outcome of Endoscopic Submucosal Dissection for Papillary Type Early Gastric Cancer: A Multicenter Study

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Background/Aims: Papillary adenocarcinoma is classified to differentiated-type gastric cancer and is indicated for endoscopic submucosal dissection. However, due to its rare nature, there are limited studies on it. The purpose of this study was to determine the outcome of endoscopic submucosal dissection in patients with papillary-type early gastric cancer and to find the risk factors of lymph node metastasis.

Methods: Patients diagnosed with papillary-type early gastric cancer at eight medical centers, who underwent endoscopic submucosal dissection or surgical treatment, were retrospectively reviewed. The clinical results and long-term outcomes of post-endoscopic submucosal dissection were evaluated, and the risk factors of lymph node metastasis in the surgery group were analyzed.

Results: One-hundred and seventy-six patients with papillary-type early gastric cancer were enrolled: 44.9% (n=79) in the surgery group and 55.1% (n=97) in the endoscopic submucosal dissection group. As a result of endoscopic submucosal dissection, the *en bloc* resection and curative resection rates were 91.8% and 86.6%, respectively. The procedure-related complication rate was 4.1%, and local recurrence occurred in 3.1% of patients. Submucosal invasion (odds ratio, 3.735; 95% confidence interval, 1.026 to 12.177; p=0.047) and lymphovascular invasion (odds ratio, 7.636; 95% confidence interval, 1.730 to 22.857; p=0.004) were the risk factors of lymph node metastasis in papillary-type early gastric cancer patients.

Conclusions: The clinical results of endoscopic submucosal dissection in papillary-type early gastric cancer were relatively favorable, and endoscopic submucosal dissection is considered safe if appropriate indications are confirmed by considering the risk of lymph node metastasis. (Gut Liver, Published online August 14, 2023)

Key Words: Papillary adenocarcinoma; Endoscopic submucosal dissection; Lymph node metastasis

INTRODUCTION

Endoscopic submucosal dissection (ESD) is recommended as the primary treatment for patients with early gastric cancer (EGC) without lymph node (LN) metastasis.¹ Compared to conventional surgical treatment, ESD

is a minimally invasive procedure that can preserve the stomach with the advantage of reducing morbidity or complications caused by surgery. With the development of procedure techniques and equipment, the use of ESD procedures is gradually increasing.^{2,3} Studies analyzing clinical outcomes after ESD in patients with absolute indication as

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well as patients with expanded indication show favorable outcomes, indicating that ESD indications are gradually expanding.^{4,5} However, unlike surgery, ESD has the limitation that LN resection or metastasis cannot be confirmed; therefore, the risk of LN metastasis remains a concern during ESD.⁶

Papillary adenocarcinoma is one of the histological classifications of gastric cancer and is a rare type that accounts for approximately 6% to 11% of all gastric cancers.^{7,8} Pathologically, it is characterized by elongated epithelial protrusions and a thin fibrous core, and the Japanese guidelines classify it as differentiated-type gastric cancer, while the Lauren classification defines it as intestinal-type.^{9,10} Therefore, the Japanese guidelines apply the same ESD indications as other differentiated-type EGC. However, due to the rare incidence of papillary adenocarcinoma, there are difficulties in enrolling patients for studies, and research on this topic is still lacking.⁹ Even though there have been many ESD studies targeting differentiated-type EGC patients, the number of papillary-type EGC patients included is extremely small.¹¹ In addition, papillary gastric adenocarcinoma has a high risk for hepatic and LN metastases. A study showed that the 5-year survival rate of papillary-type EGC is lower than that of non-papillary gastric cancer; therefore, the indications for ESD in papillary-type EGC patients remain controversial.^{12,13} The purpose of this study was to analyze the clinical results and long-term outcomes after ESD in papillary-type EGC, and to determine the risk factors of LN metastasis to confirm whether ESD can be applied in papillary-type EGC.

MATERIALS AND METHODS

1. Patients

The medical charts of patients who were histologically diagnosed with papillary-type EGC and underwent ESD or surgery at eight medical centers between January 2012 and December 2020 were retrospectively analyzed. Patients who refused treatment after gastric cancer diagnosis or were transferred to another hospital were excluded. According to the treatment method, the patients were classified into either the ESD or surgery group. The clinical outcome after ESD was analyzed and the risk factors were identified by dividing the patients in the surgery group into two groups according to LN metastasis. For clinical staging before treatment, chest radiography and abdominal computed tomography were performed in all patients diagnosed with papillary-type EGC. The upper, middle, and lower thirds were classified according to site of the tumor in the stomach, and elevated, flat and depressed

types were classified according to endoscopic macroscopic findings. The study protocol was approved by the Institutional Review Board of Chungnam National University Sejong Hospital (IRB number: 2021-05-019). This study is a retrospective study using medical charts review and so informed consent was waived.

2. ESD, surgery procedure and pathologic evaluation

All ESD procedures were performed by expert university hospital endoscopists. Midazolam or propofol was injected intravenously to sedate the patient with cardiopulmonary monitoring. ESD was performed using an existing standardized method. If necessary, the boundaries of the lesion were confirmed using chromoendoscopy (indigo carmine or narrow band imaging) and marked with argon plasma coagulation at a sufficient distance around the tumor. In addition, saline solution containing epinephrine and indigo carmine was injected and the lesion was dissected with insulation-tipped diathermy knife or insulation-tipped knife-2 (Olympus Medical, Tokyo, Japan).

According to the tumor location, size, and macroscopically determined EGC type, total or subtotal gastrectomy was performed. For curative resection, at least 3 cm was left as a resection margin from the tumor and extended D2-lymphadenectomy was performed. The resected tissue was fixed in formalin, and then serial sectioning was performed to check the lateral and basal margins under a microscope. When two or more pathological types were mixed, papillary adenocarcinoma was defined only when >50% had a papillary component, and it was classified separately as a mixed papillary-type group.¹⁴ Pathologic staging was confirmed, including of tumor size, invasion depth, lymphovascular invasion (LVI), ulcers, and lateral and basal margin involvement.

3. Definition

En bloc resection is a case in which one piece is resected at once as a result of endoscopic resection. Curative resection is defined as the absence of tumor involvement in the lateral and basal margins of *en bloc* resected tissues and absence of LVI: (1) tumor size ≤ 2 cm, mucosal cancer, no ulcer in the tumor; (2) tumor size > 2 cm, mucosal cancer, no ulcer in the tumor; (3) tumor size ≤ 3 cm, mucosal cancer, ulcer in the tumor; or (4) tumor size ≤ 3 cm, SM1 cancer (submucosal invasion depth < 500 μ m from the muscularis mucosa layer). Among the above, number 1 was defined as an absolute indication, and numbers 2 to 4 were defined as expanded indications. Piecemeal resected tissue was defined as curative resection if the lateral and basal margins could be sufficiently identified after the reconstruction. Bleeding was defined as when the patient has symptoms

such as melena or hematochezia after the procedure, fall of hemoglobin level (>2 g/dL), or when additional hemostasis is performed. Perforation was defined as when an operator discovered it during an ESD procedure, or when free air was visible on a post-procedure radiograph.

Local recurrence was defined as a case in which another cancer was found at the primary resection site during the follow-up endoscopy performed after ESD. Synchronous lesions were defined as those occurring within 12 months from the date of the primary ESD procedure, while metachronous lesions were defined as those occurring after 12 months. During the follow-up period, all patients were analyzed for recurrence, location of recurrence, secondary treatment, and overall survival.

4. Follow-up

After the ESD procedure, complete blood cell counts, chest radiography, and abdominal radiography were performed to check for complications. In cases where the resection was non-curative, additional treatment (secondary ESD or surgery) was immediately performed. In the case of curative resection, endoscopy was performed 2 months later to confirm healing of the ESD ulcer and assess the presence of a remnant tumor. Subsequently, endoscopy, abdominal computed tomography, and radiographic surveillance were performed at 6- to 12-month intervals, and the interval was determined according to the patient's status.

5. Statistical analysis

The chi-square test was performed to compare and analyze categorical variables. Continuous variables are presented as mean and standard deviation. For the multivariate analysis, logistic regression was used, and the results are presented as odds ratios (OR) and confidence intervals (CI). *p*-values were two-sided, and a value less than 0.05 was considered statistically significant. All statistical analy-

ses were conducted using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

1. Clinical characteristics of papillary-type EGC patients

In this study, a chart review was conducted on 231 papillary-type gastric cancer patients, and 176 patients with papillary-type EGC were enrolled, excluding cases that did not meet the selection criteria. When classified according to the treatment method, 44.9% ($n=79$) were in the surgery group and 55.1% ($n=97$) in the ESD group (Fig. 1). The clinical characteristics of all papillary-type EGC patients are shown in Table 1. Regarding sex, 70.5% ($n=124$) were male, and the mean age was 71.9 ± 8.7 years. Classification according to tumor location was as follows: lower third (59.7%), middle third (28.4%), and upper third (11.9%). Regarding the endoscopic macroscopic type, the elevated type was the most common at 60.8% ($n=107$), followed by the flat type at 19.9% ($n=35$), and the depressed type at 19.3% ($n=34$). Tumors were confined to the mucosa in 63.1% ($n=111$) of cases, and submucosal invasion was confirmed in 36.9% (32 SM1, 25 SM2, and 8 SM3). The mean tumor size was 22.6 ± 10.3 mm, and ulcers were observed

Table 1. Clinical Characteristics of Papillary Type Early Gastric Cancer Patients

Characteristic	No. [%] ($n=176$)
Male sex	124 [70.5]
Age, mean \pm SD, yr	71.9 \pm 8.7
Tumor location	
Upper third	21 [11.9]
Middle third	50 [28.4]
Lower third	105 [59.7]
Macroscopic type	
Elevated	107 [60.8]
Flat	35 [19.9]
Depressed	34 [19.3]
Histologic type	
Pure papillary type	123 [69.9]
Mixed papillary type	53 [30.1]
Depth of invasion	
Mucosa	111 [63.1]
Submucosa	65 [36.9]
Tumor size, mean \pm SD, mm	22.6 \pm 10.3
Treatment methods	
Surgery	79 [44.9]
Endoscopic submucosal dissection	97 [55.1]
Present of ulcer	36 [20.5]
Lymphovascular invasion	40 [22.7]

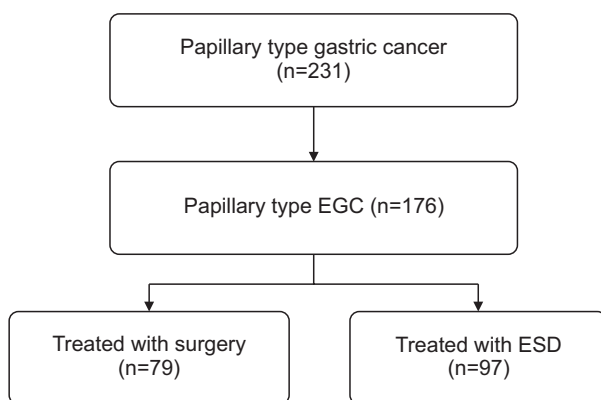


Fig. 1. Flowchart of this study.
EGC, early gastric cancer; ESD, endoscopic submucosal dissection.

Table 2. Endoscopic Submucosal Dissection Results in Papillary Type Early Gastric Cancer Patients

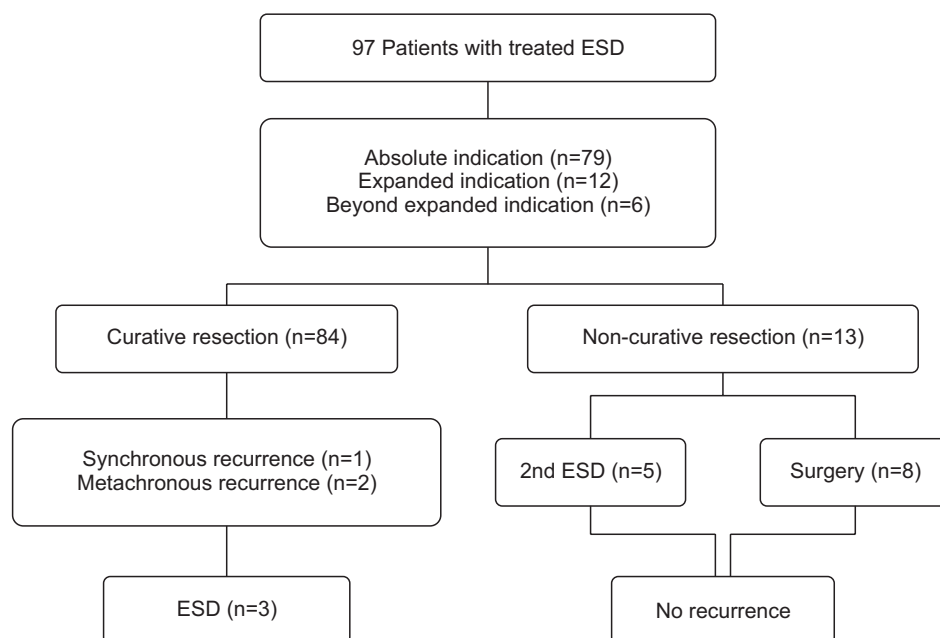
Characteristic	Total patients (n=97)	Mucosal cancer (n=79)
Male sex	79 (81.4)	51 (64.6)
Age		
≤70 yr	41 (42.3)	34 (43.0)
>70 yr	56 (57.7)	45 (57.0)
Tumor location		
Upper third	10 (10.3)	6 (7.6)
Middle third	22 (22.7)	20 (25.3)
Lower third	65 (67.0)	53 (67.1)
Macroscopic type		
Elevated	58 (59.8)	46 (58.2)
Flat	22 (22.7)	21 (26.6)
Depressed	17 (17.5)	12 (15.2)
Histologic type		
Pure papillary type	66 (68.0)	57 (72.2)
Mixed papillary type	31 (32.0)	22 (27.8)
Tumor size		
≤15 mm	56 (57.7)	49 (62.0)
>15 mm	41 (42.3)	30 (38.0)
Present of ulcer	4 (4.1)	
Lymphovascular invasion	5 (5.2)	2 (2.5)
Resection margin positive	9 (9.3)	3 (3.8)
<i>En bloc</i> resection	89 (91.8)	72 (91.1)
Curative resection	84 (86.6)	74 (93.7)
Complication	4 (4.1)	2 (2.5)
Bleeding	4 (4.1)	2 (2.5)
Perforation	0	0
Local recurrence	3 (3.1)	1 (1.3)
Death	0	0

Data are presented as number (%).

in 36 patients (20.5%). Of all patients with papillary-type EGC, 22.7% (n=40) had LVI.

2. Post-ESD outcomes in papillary-type EGC patients

ESD results of patients with papillary-type EGC are shown in Table 2. Among the 97 patients who underwent ESD, 79 (81.4%) were men. The lesions were mainly located in the lower third (67.0%), and elevated type (59.8%) was the most common. In more than half of patients, the tumor size was ≤15 mm (57.7%), and ulcers were present in four patients (4.1%). LVI was observed in five patients (5.2%), and tumors were involved at the resection margin in nine patients (9.3%) (2 lateral, 5 basal, and 2 both). *En bloc* resection rate was 91.8% (n=89) and the curative resection rate was 86.6% (n=84). Procedure-related complications occurred in four patients (4.1%), all of whom had minor bleeding. During the mean follow-up period of 50.3±16.7 months, local recurrence occurred in three patients (3.1%), and no patient died. The ESD clinical outcomes of 79 patients whose tumors were confined to the mucosa were analyzed as a subgroup. Baseline characteristics were not significantly different from the data of all patients but showed a more favorable post-ESD clinical outcome. The curative resection rate (93.7% vs 86.6%, $p=0.197$) was higher in the mucosal cancer group than that in the total patient group, and procedure-related complications (2.5% vs 4.1%, $p=0.872$) and local recurrence (1.3% vs 3.1%, $p=0.748$) were less common. However, these differences did not reach statistical significance. When comparing the mucosal and submucosal groups, the curative resection rates were 93.7% versus 55.6% ($p=0.000$),

**Fig. 2.** Long-term outcome of papillary type early gastric cancer (EGC) patients treated with endoscopic submucosal dissection (ESD).

procedure-related complication rates were 2.5% versus 11.1% ($p=0.320$), and local recurrence rates were 1.3% versus 11.1% ($p=0.155$). In the submucosal group, there were two cases in which SM2 invasion were detected, and the ESD results showed marginal involvement in all cases. The long-term outcomes of patients with papillary-type EGC treated with ESD are shown in Fig. 2. Among 97 patients with papillary-type EGC who underwent ESD, 79 (81.4%) had absolute indications, 12 (12.4%) had expanded indications, and six (6.2%) had beyond expanded indications. As a result of ESD, 84 patients underwent curative resection and 13 patients underwent non-curative resection. Causes of non-curative resection were resection margin involvement in eight cases, LVI in four cases, and both at the same time in one case. In the curative resection group, synchronous recurrence was found in one patient and metachronous recurrence was found in two patients, all of whom were followed up after ESD. In the non-curative resection group, additional treatment was immediately performed; therefore, five patients underwent secondary ESD and eight underwent surgery and were followed up

without recurrence. Additional treatment results of the 13 non-curative resection patients, three had LVI and one had LN metastasis. There were no papillary-type EGC-related deaths in any of the patients.

3. Risk factors of LN metastasis

Risk factors were analyzed by dividing the 79 patients who performed surgery for papillary-type EGC into two groups according to LN metastasis (Table 3). Overall LN metastasis rate was 19.0% ($n=15$). There were no significant differences in sex, age, and tumor location between the LN metastasis group and the group without LN metastasis. When classified according to the endoscopic findings, in the LN metastasis group, elevated type was most common at 80.0% ($n=12$), and in the group without LN metastasis, elevated type was the most at 57.8% ($n=37$). The pure papillary type was more dominant in the histological type, but there was no significant difference between the two groups ($p=0.837$). Submucosal invasion was significantly higher in the LN metastasis group than that in the group without LN metastasis (86.7% vs 53.1%, $p=0.036$). In both

Table 3. Risk Factors for LNM in Papillary Type Early Gastric Cancer Patients

Characteristic	LNM (+) (n=15)	LNM (-) (n=64)	p-value	Multivariate analysis	
				OR (95% CI)	p-value*
Male sex	12 (80.0)	49 (76.6)	0.954		
Age			0.508		
≤70 yr	5 (33.3)	30 (46.9)			
>70 yr	10 (66.7)	34 (53.1)			
Tumor location			0.710		
Upper third	1 (6.7)	10 (15.6)			
Middle third	6 (40.0)	22 (34.4)			
Lower third	8 (53.3)	32 (50.0)			
Macroscopic type			0.294		
Elevated	12 (80.0)	37 (57.8)			
Flat	0	13 (20.3)			
Depressed	3 (20.0)	14 (21.9)			
Histologic type			0.837		
Pure papillary type	10 (66.7)	47 (73.4)			
Mixed papillary type	5 (33.3)	17 (26.6)			
Depth of invasion			0.036		
Mucosa	2 (13.3)	30 (46.9)		Reference (1.000)	
Submucosa	13 (86.7)	34 (53.1)		3.735 (1.026–12.177)	0.047
Tumor size			0.980		
≤30 mm	8 (53.3)	37 (57.8)			
>30 mm	7 (46.7)	27 (42.2)			
Ulcer			0.357		
Absent	11 (73.3)	36 (56.3)			
Present	4 (26.7)	28 (43.7)			
Lymphovascular invasion			0.001		
Absent	0	44 (68.7)		Reference (1.000)	
Present	15 (100)	20 (31.3)		7.636 (1.730–22.857)	0.004

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval.

*Adjusted for depth of invasion and lymphovascular invasion.

groups, more than half of the cases had a tumor size of ≤ 30 mm (53.3% vs 57.8%, $p=0.980$) and cases without ulcers were predominant, but there was no statistically significant difference ($p=0.357$). LVI was significantly higher in the LN metastasis group than that in the group without LN metastasis (100.0% vs 31.3%, $p=0.001$).

Multivariate analysis was performed by adjusting for the depth of invasion and LVI, which showed differences between the two groups on univariate analysis. Submucosal invasion (OR, 3.735; 95% CI, 1.026 to 12.177; $p=0.047$) and LVI (OR, 7.636; 95% CI, 1.730 to 22.857; $p=0.004$) were significant risk factors of LN metastasis in papillary-type EGC patients.

DISCUSSION

Among the 176 patients with papillary-type EGC enrolled in this study, 79 were in the surgery group and 97 were in the ESD group. LN metastasis was present in 19.0% ($n=15$) of the patients in the surgery group, and submucosal invasion or LVI was a significant risk factor of LN metastasis. Among the 97 patients in the ESD group, 79 (81.4%) had absolute indications, 12 (12.4%) had expanded indications, and six (6.2%) had beyond expanded indications. Most papillary-type EGC patients underwent curative resection as a result of ESD (86.6%), and 13 patients who underwent non-curative resection underwent secondary ESD ($n=5$) or additional surgery ($n=8$). As a result of a long-term follow-up with a mean of 50.3 ± 16.7 months, recurrence was observed in three patients in the ESD group, all of whom were treated with ESD.

Papillary adenocarcinoma is a rare disease that accounts for $<10\%$ of all gastric cancers and has an incidence of approximately 1%, especially in EGC.^{15,16} The prognosis is poor because of considerable submucosal invasion and LN metastasis even in the early stages. However, because of its rare nature, there are limited studies on this topic.^{12,17} In this study, the elevated type was the most common with 60.5% of all papillary-type EGC patients, showing similar results to those of previous studies.

Compared to surgery, ESD, which has several advantages, is considered first-line treatment methods for patients with EGC, if indicated.^{1,9} Papillary adenocarcinoma is classified as differentiated-type gastric cancer in the Japanese guideline.⁹ ESD showed satisfactory treatment results in patients with differentiated-type EGC, and high curative resection results (85% to 95%) and favorable survival rate (5-year survival rate 95% to 100%) were reported.^{18,19} According to recent studies, papillary-type EGC showed similar results as those of differentiated-type EGC

after ESD. In a review analyzing 15 studies, *en bloc* resection, complete resection, and curative resection rates were 89.7% (95% CI, 55.3% to 98.4%), 85.3% (95% CI, 67.7% to 94.2%), and 67% (95% CI, 43% to 84.5%), respectively, and there was no LN metastasis in curative resection patients.²⁰ In another study that analyzed the ESD results of 87 patients with papillary-type EGC, patients who underwent curative resection were followed up for a median of 58 months, and no extragastric recurrence was observed.²¹ In this study, the *en bloc* resection and curative resection rates were 91.8% and 86.6%, respectively, and 91.1% and 93.7%, respectively, in the case of mucosal cancer. In addition, procedure-related bleeding occurred in 4.1% ($n=4$) of 97 patients in the ESD group. However, minor bleeding with endoscopic bleeding control was possible, and there was no perforation. As a result of follow-up for an mean of 50.3 ± 16.7 months, a satisfactory long-term outcome was shown, and local recurrence was found in 3.1% ($n=3$), but all were treated with ESD with no fatality. As such, ESD in patients with papillary-type EGC is considered a relatively safe procedure with favorable clinical results and long-term outcomes if indicated.

In patients with EGC, surgery is performed after ESD because of non-curative resection or procedure-related complications. The incidence of ESD after surgery has been reported to range from 2.1% to 14.6% and is caused by lateral or basal margin involvement, presence of LVI, deep submucosal invasion, undifferentiated-type histology, or procedure-related complications.^{22,23} In this study, additional surgery was performed in 8.2% ($n=8$) of 97 papillary-type EGC patients who underwent ESD. The reasons for surgery were non-curative resection, with LVI in two patients, basal resection margin involvement in four patients, and deep submucosal invasion in two patients. Therefore, the incidence of ESD after surgery was similar to that in conventional EGC patients with papillary-type EGC.

Among the various factors that determine the indications for ESD in EGC patients, LN metastasis risk is the most important factor, and deep submucosal invasion, LVI, undifferentiated-type histology, and larger tumor size are known risk factors of LN metastasis.²⁴ In general, the incidence of LN metastasis in EGC patients is 5% to 10% (0%–4% for mucosal cancer vs 2%–19% for submucosal cancer; 2%–9% for differentiated-type cancer vs 3%–10% for undifferentiated-type cancer), but there are differences between studies.^{9,25} In one study that analyzed the LN metastasis risk factor in 49 patients of papillary-type EGC, the prevalence of LN metastasis was 7.1% in mucosal invasion cancer and 22.9% in submucosal invasion cancer, and LVI was a risk factor of LN metastasis.²⁶ In another study, LN

metastasis was confirmed in 13 of 52 patients (25%) with papillary-type EGC.²⁷ In this study, LN metastasis was observed in 15 of 79 patients (19.0%) in the surgery group. In patients with mucosal cancer, the rate of LN metastasis was 6.3% (2/32). When compared to differentiated cancer, it tends to be slightly higher, but compared to studies targeting papillary EGC, there is no significant difference, and the small sample size is also thought to be the cause. The independent risk factors of LN metastasis in papillary-type EGC patients were submucosal invasion (OR, 3.735; 95% CI, 1.026 to 12.177; $p=0.047$) and LVI (OR, 7.636; 95% CI, 1.730 to 22.857; $p=0.004$). Patients with papillary-type EGC with these risk factors require careful follow-up after ESD.

The limitations of this study were as follows. First, because of the retrospective nature, it is difficult to generalize our study results. However, efforts have been made to reduce these limitations by enrolling patients in several number of medical centers. Second, there is a possibility of bias in treatment methods or management between operators or medical centers. However, it is considered that all ESD procedures are performed in a standardized manner by expert gastrointestinal endoscopists, which may result in minimal differences. The strength of this study is that it is the first multicenter study in which a large number of patients were enrolled. And the difference from previous studies is that ESD and surgery results were analyzed at the same time.

This study implies that ESD treatment is a relatively safe procedure with favorable short- and long-term outcomes in patients with papillary-type EGC if appropriate indications are followed. However, if submucosal invasion or LVI is present, careful observation is required to rule out the possibility of LN metastasis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: J.S.K., H.D.S. Data acquisition; statistical analysis: K.B.B., S.H.K., H.S.M., J.K.S., H.Y.J., D.K.L., K.B.K., S.M.K., S.W.L., D.S.L., Y.S.C., I.K.C. Data analysis and interpretation: K.B.B., S.H.K., H.S.M., J.K.S., H.Y.J., D.K.L., K.B.K., S.M.K., S.W.L., D.S.L., Y.S.C., I.K.C. Drafting of the manuscript: K.B.B., S.H.K., H.S.M., J.K.S., H.Y.J., D.K.L., K.B.K., S.M.K., S.W.L., D.S.L., Y.S.C., I.K.C.

Critical revision of the manuscript for important intellectual content: J.S.K., H.D.S. Administrative, technical, or material support; study supervision: H.D.S. Approval of final manuscript: all authors.

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