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ORIGINAL ARTICLE

Lymphovascular invasion and lymph node metastasis rates in papillary adenocarcinoma of the stomach: implications for endoscopic resection

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Abstract

Background Current Japanese gastric cancer treatment guidelines recommend the same endoscopic resection criteria for papillary early gastric cancer (EGC) and well-differentiated (WD) or moderately differentiated (MD) EGC. To evaluate the appropriateness of this recommendation, we compared the clinicopathological characteristics of papillary EGC with those of WD, MD, poorly differentiated (PD), and signet ring cell (SRC) EGC.

Methods A total of 6710 patients who underwent radical gastrectomy for EGC were included. Clinicopathological characteristics of papillary EGC were retrospectively reviewed and compared with those in other EGC subtypes.

Results Papillary EGC accounted for 1.9% (130/6710) of total cases. Patients with papillary EGC were older and showed a male predominance compared to patients with PD or SRC EGC. Papillary EGCs showed significantly higher submucosal and lymphovascular invasion rates than WD or MD EGC or PD or SRC EGC. However, the LN metastasis rate of papillary EGC was comparable to or lower than that in other EGC subtypes. LN metastasis rates in mucosal cancers were 1.5%, 1.1%, and 4.0%, and those in submucosal cancers were 9.4%, 11.9%, and 17.6% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively. In multivariate analysis, lymphatic invasion and PD or SRC histology were the strongest risk factors for LN metastasis. Among 63 papillary EGC that met the curative endoscopic resection criteria, no case showed LN metastasis.

Conclusions Endoscopic resection can be indicated for papillary EGC according to current guidelines. Given a considerable lymphovascular invasion rate, careful histological evaluation is required after endoscopic resection for papillary EGC.

Keywords Papillary adenocarcinoma · Early gastric cancer · Lymph node metastasis · Lymphovascular invasion

Introduction

Papillary adenocarcinoma of the stomach is defined as a well-differentiated exophytic gastric carcinoma with elongated finger-like processes lined by cylindrical or cuboidal cells supported by fibromuscular connective tissue cores [1]. As papillary adenocarcinoma is a rare subtype of gastric adenocarcinoma, its clinicopathological characteristics and biological behavior remain unclear [2, 3]. In Japanese classification, papillary adenocarcinoma and well-differentiated (WD) or moderately differentiated (MD) tubular adenocarcinoma are classified together as differentiated-type gastric carcinoma, and the same endoscopic resection criteria are applied in cases of early gastric cancer (EGC) [4]. However, several recent studies have shown that patients with papillary EGC have a higher lymphovascular invasion rate and worse prognosis compared to undifferentiated-type as

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well as other differentiated-type EGCs [2, 5–9]. This higher lymphovascular invasion rate raised concerns that papillary EGC might have a considerable lymph node (LN) metastasis rate and that current endoscopic resection criteria might be inappropriate for papillary EGC. In fact, recent Japanese and Korean studies reported a higher LN metastasis rate in papillary EGC compared to other subtypes of EGC in univariate analysis [2, 6, 7]. In a Japanese study, however, the papillary component was not an independent risk factor for LN metastasis in EGC [7].

In the present study, we aimed to identify the clinicopathological characteristics of papillary EGC and to evaluate whether papillary EGC is associated with a higher risk of LN metastasis compared to other subtypes of EGC.

Methods

Patients

From May 2004 to November 2015, 7573 patients with EGC underwent radical gastrectomy with LN dissection at Samsung Medical Center. Among these patients, the following cases were excluded from the study population: 349 patients with multiple synchronous EGCs, 55 patients with EGC arising from the remnant stomach, 21 patients with missing data, 33 patients with lymphoepithelioma-like carcinoma, 20 patients with mucinous adenocarcinoma, 1 patient with hepatoid adenocarcinoma, and 384 patients undergoing additional surgery after endoscopic resection for submucosal EGC. In our institute, the submucosal invasion depth of the surgical specimen was reported using a three-tier system: SM1, SM2, and SM3 representing invasion of cancer cells into the upper third, middle third, and lower third of the submucosa, respectively [10]. As this system cannot be applied to endoscopic resection specimens that do not contain the whole submucosal layer, we excluded submucosal EGC cases initially treated with endoscopic resection. After exclusions, a total of 6710 patients with EGC were ultimately included in the study population. In Korean and Japanese guidelines [4, 11, 12], EGC consisting of components of both differentiated-type and undifferentiated-type carcinoma [including poorly differentiated (PD) adenocarcinoma, signet ring cell (SRC) carcinoma, and mucinous adenocarcinoma] is classified according to the quantitatively predominant histological type. Accordingly, papillary adenocarcinoma is defined as a tumor in which more than 50% of the tumor area contains papillary structures composed of epithelial projections with a central fibrovascular core as a scaffold in the present study. Clinicopathological data including demographic features, tumor characteristics, and LN metastasis were obtained by the retrospective review of medical records using the intranet resources of Samsung Medical Center. All patients provided informed consent according to our institutional guidelines. The institutional review board of Samsung Medical Center approved the study protocol.

Histopathological evaluation

Specimens were fixed in 10% formalin and then serially sectioned at 5-mm intervals, embedded in paraffin blocks, and stained with hematoxylin and eosin. A tumor was considered as positive for lymphovascular invasion when tumor emboli were found within a space that was clearly lined by endothelial cells. The lymph nodes were cut into two pieces, and the cut surfaces were examined to determine the status of the nodes. Lymph node metastasis was identified using hematoxylin and eosin staining [13].

For papillary EGC cases, nuclear atypia grade was determined as low or high grade according to nuclear polymorphism and nuclear polarity observed in cancer cells (Fig. 1) [14]. We also investigated the presence of undifferentiated component in papillary EGC cases.

Statistical analysis

Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Continuous variables were analyzed using Student's *t* test. Survival rates were calculated using the Kaplan–Meier method. To identify independent predictive factors for LN metastasis, multivariate binary logistic regression analysis was performed. The odds ratios and 95% confidence intervals were calculated. A P value less than 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of early gastric papillary adenocarcinoma versus nonpapillary adenocarcinoma

The study population included 130 patients with papillary EGC (1.9%, 130/6710), 2711 patients with WD or MD EGC (40.4%, 2711/6710), and 3869 patients with PD or SRC EGC (57.7%, 3869/6710). The mean age of the study population was 55.8 ± 11.5 years. The proportions of submucosal EGC were 49.2%, 38.2%, and 31.1% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively ($P < 0.001$).

Table 1 summarizes and compares the clinicopathological characteristics of papillary EGC and nonpapillary EGC confined to the mucosal layer. Patients with papillary EGC were older than those with WD or MD EGC or PD or SRC EGC and showed a male predominance compared to those with PD or SRC EGC. Papillary EGCs were larger and more

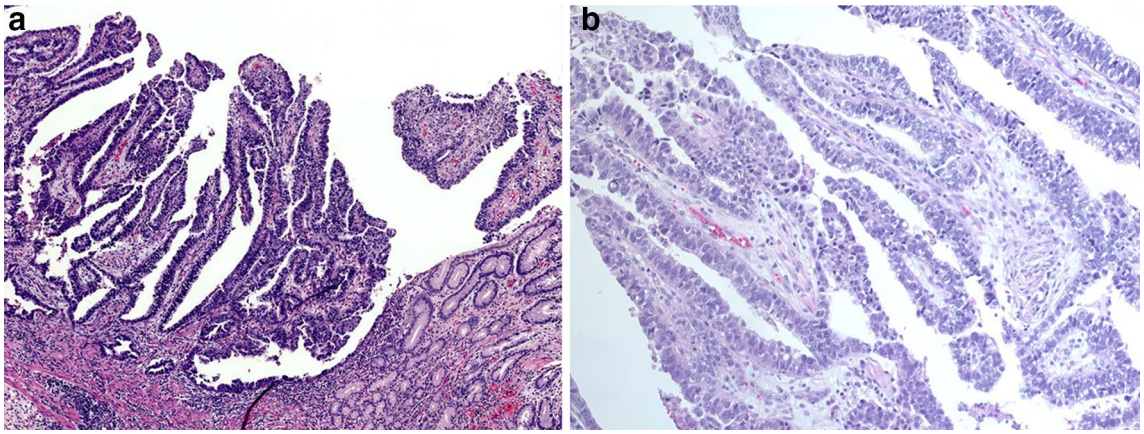

Fig. 1 A case of papillary gastric adenocarcinoma with high-grade nuclear atypia. **a** Low-magnification view [hematoxylin and eosin (H&E), ×40]. **b** High-magnification view (H&E, ×400)

frequently elevated in macroscopic type and showed significantly higher lymphatic and venous invasion rate than WD or MD EGC or PD or SRC EGC. LN metastasis rates in mucosal cancers were 1.5%, 1.1%, and 4.0% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively.

Table 2 summarizes and compares the clinicopathological characteristics of papillary EGC and nonpapillary EGC with submucosal invasion. Patients with papillary EGC were older and showed a male predominance compared to patients with PD or SRC EGC. Patients with papillary EGCs more frequently had a macroscopically elevated tumor and showed significantly higher lymphatic and venous invasion rate than those with WD or MD EGC or PD or SRC EGC. LN metastasis rates in submucosal cancers were 9.4%, 11.9%, and 17.6% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively.

Predictive factors associated with lymph node metastasis in patients with early gastric cancer

Table 3 shows the results of univariate and multivariate analysis of clinicopathological characteristics associated with LN metastasis in 6710 EGCs. Multivariate analysis revealed that younger age, female sex, lower third tumor location, large tumor size, submucosal invasion, PD adenocarcinoma or SRC carcinoma histology, and the presence of lymphatic invasion were independent predictive factors for LN metastasis. LN metastasis rates in the total study population were 5.4%, 5.2%, and 8.3% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively.

In the total study population, lymphatic invasion rates were 26.2%, 13.6%, and 9.9% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively. In patients with lymphatic invasion, LN metastasis rates were 14.7%, 26.2%, and 39.3% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively. In the total study population, venous invasion rates were 7.7%, 1.6%, and 0.5% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively. No papillary EGC patient with venous invasion showed distant metastasis at the time of surgery or during follow-up period. In patients with venous invasion, LN metastasis rates were 10.0%, 27.9%, and 33.3% for papillary EGC, WD or MD EGC, and PD or SRC EGC, respectively.

Clinicopathological characteristics of patients with early gastric papillary adenocarcinoma with lymph node metastasis

Table 4 summarizes the results of univariate analysis of clinicopathological characteristics associated with LN metastasis in 130 papillary EGCs. Papillary EGCs with LN metastasis showed significantly higher rates of tumor size larger than 3.0 cm, deep submucosal invasion, and lymphatic invasion than tumors without LN metastasis. Multivariate analysis could not be performed as the model was not fitted because of the small number of patients with LN metastasis. Among seven papillary EGC patients with LN metastasis (Table 5), six patients (85.7%) had tumors with deep submucosal invasion (SM2 or SM3), and only one patient (14.3%) had mucosal cancer. Tumor size was larger than 3.0 cm in all cases, and lymphatic invasion was present in five cases (71.4%). The mucosal cancer with LN metastasis was 5.5 cm in size and had lymphatic invasion; thus, it did not meet the curative endoscopic resection criteria [4].

Among 130 papillary EGCs, 57 mucosal EGCs and 6 submucosal EGCs met the curative endoscopic resection criteria proposed in the Japanese gastric cancer treatment guidelines [4]. None of these tumors showed LN metastasis in the surgical specimen. The submucosal invasion depth of 6 submucosal EGCs ranged from 50 to 400 μm.

Table 1 Clinicopathological characteristics of early gastric papillary adenocarcinoma versus nonpapillary adenocarcinoma confined to mucosal layer

Characteristic	Papillary adenocarcinoma ($n = 66$)	WD or MD adenocarcinoma ($n = 1676$)	*P value	PD adenocarcinoma or SRC carcinoma ($n = 2667$)	*P value
Age (years)			<0.001		<0.001
Mean ± SD	65.6 ± 9.4	59.7 ± 10.3		51.5 ± 11.0	
Gender (%)			0.755		<0.001
Male	50 (75.8)	1241 (74.0)		1372 (51.4)	
Female	16 (24.2)	435 (26.0)		1295 (48.6)	
Tumor site (%)			0.142		0.001
Upper third	5 (7.6)	139 (8.3)		227 (8.5)	
Middle third	9 (13.6)	398 (23.7)		931 (34.9)	
Lower third	52 (78.8)	1139 (68.0)		1509 (56.6)	
Macroscopic type (%)			<0.001		<0.001
Elevated	34 (51.5)	274 (16.3)		81 (3.0)	
Flat/depressed	32 (48.5)	1402 (83.7)		2586 (97.0)	
Ulcer (%)			1.000		0.725
Absent	65 (98.5)	1630 (97.3)		2576 (96.6)	
Present	1 (1.5)	46 (2.7)		91 (3.4)	
Tumor size (cm)			0.004		0.050
Mean ± SD	3.0 ± 1.2	2.4 ± 1.6		2.7 ± 1.8	
Lymphatic invasion (%)			0.002		0.001
Absent	58 (87.9)	1619 (96.6)		2596 (97.3)	
Present	8 (12.1)	57 (3.4)		71 (2.7)	
Venous invasion (%)			0.001		<0.001
Absent	63 (95.5)	1674 (99.9)		2664 (99.9)	
Present	3 (4.5)	2 (0.1)		3 (0.1)	
Perineural invasion (%)			0.109		0.137
Absent	65 (98.5)	1674 (99.9)		2662 (99.8)	
Present	1 (1.5)	2 (0.1)		5 (0.2)	
Lymph node metastasis (%)			0.540		0.519
Absent	65 (98.5)	1657 (98.9)		2559 (96.0)	
Present	1 (1.5)	19 (1.1)		108 (4.0)	

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *SRC* signet ring cell, *SD* standard deviation

* Compared with papillary adenocarcinoma

Nuclear atypia grade and presence of undifferentiated component in early gastric papillary adenocarcinoma

We investigated the presence of undifferentiated component and nuclear atypia grade in 118 papillary EGCs for which pathological slides were available. No papillary EGC case showed an undifferentiated component. For nuclear atypia grade, 46 (39.0%) were classified as tumor with low-grade nuclear atypia and 72 (61.0%) as tumor with high-grade nuclear atypia. No significant difference was found in lymphatic invasion and LN metastasis rates between papillary EGCs with low-grade nuclear atypia and high-grade nuclear atypia (Table 6).

Discussion

To achieve curative resection through endoscopic resection, it is critical to select tumors with little risk of LN metastasis. In Korean and Japanese studies, extragastric recurrence rate after curative endoscopic resection for differentiated- and undifferentiated-type EGC ranged from 0.10% to 0.15% [15–18], which is acceptable considering postoperative morbidity and mortality after radical gastrectomy. Papillary adenocarcinoma is classified as a differentiated-type gastric carcinoma, and current Japanese gastric cancer treatment guidelines recommend the same endoscopic resection criteria for papillary EGC and WD or MD EGC [4]. However, several recent studies have reported that patients with

Table 2 Clinicopathological characteristics of early gastric papillary adenocarcinoma versus nonpapillary adenocarcinoma with submucosal invasion

Characteristic	Papillary adenocarcinoma ($n = 64$)	WD or MD adenocarcinoma ($n = 1035$)	*P value	PD adenocarcinoma or SRC carcinoma ($n = 1202$)	*P value
Age (years)			0.155		<0.001
Mean ± SD	63.4 ± 8.9	61.6 ± 9.9		54.2 ± 11.4	
Gender (%)			0.069		0.027
Male	44 (68.8)	812 (78.5)		657 (54.7)	
Female	20 (31.3)	223 (21.5)		545 (45.3)	
Tumor site (%)			0.212		0.001
Upper third	5 (7.8)	157 (15.2)		175 (14.6)	
Middle third	13 (20.3)	229 (22.1)		452 (37.6)	
Lower third	46 (71.9)	649 (62.7)		575 (47.8)	
Macroscopic type (%)			<0.001		<0.001
Elevated	28 (43.8)	213 (20.6)		83 (6.9)	
Flat/depressed	36 (56.3)	822 (79.4)		1119 (93.1)	
Ulcer (%)			0.668		0.765
Absent	62 (96.9)	1010 (97.6)		1143 (95.1)	
Present	2 (3.1)	25 (2.4)		59 (4.9)	
Tumor size (cm)			0.405		0.826
Mean ± SD	3.4 ± 1.6	3.2 ± 1.7		3.4 ± 2.1	
Tumor depth (%)			0.439		0.508
SM1	19 (29.7)	381 (36.8)		336 (28.0)	
SM2	25 (39.1)	336 (32.5)		406 (33.8)	
SM3	20 (31.3)	318 (30.7)		460 (38.3)	
Lymphatic invasion (%)			0.081		0.010
Absent	38 (59.4)	722 (69.8)		889 (74.0)	
Present	26 (40.6)	313 (30.2)		313 (26.0)	
Venous invasion (%)			0.018		<0.001
Absent	57 (89.1)	994 (96.0)		1187 (98.8)	
Present	7 (10.9)	41 (4.0)		15 (1.2)	
Perineural invasion (%)			0.653		0.433
Absent	62 (96.9)	1012 (97.8)		1120 (93.2)	
Present	2 (3.1)	23 (2.2)		82 (6.8)	
Lymph node metastasis (%)			0.545		0.088
Absent	58 (90.6)	912 (88.1)		990 (82.4)	
Present	6 (9.4)	123 (11.9)		212 (17.6)	

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *SRC* signet ring cell, *SD* standard deviation

* Compared with papillary adenocarcinoma

papillary EGC have higher lymphovascular invasion and LN metastasis rate compared to other subtypes of EGC [2, 6, 7], which raises concerns regarding the appropriateness of the current guidelines. In the present study including 6710 EGCs, we found papillary EGC did have a higher lymphovascular invasion rate than WD or MD EGC and PD or SRC EGC. However, the LN metastasis rate in papillary EGC was comparable or lower compared to those in WD or MD EGC or PD or SRC EGC. Furthermore, no papillary EGC showed LN metastasis if it met the curative endoscopic resection criteria. These results support current Japanese gastric cancer treatment guidelines that endoscopic resection can be indicated for papillary EGC, as in WD or MD EGC [4].

Sekiguchi et al. [7] reported results consistent with those from our study. They evaluated whether the presence of a papillary component in more than 10% of the tumor area affected the occurrence of lymphatic invasion or LN metastasis in EGC. In univariate analysis, the presence of a papillary component was significantly associated with both lymphatic invasion and LN metastasis. In multivariate analysis, the presence of a papillary component was identified as an independent risk factor for lymphatic invasion. However, the

Table 3 Multivariate analysis of clinicopathological characteristics associated with lymph node metastasis in early gastric cancers

Characteristic	Lymph node metastasis		*P* value	Odds ratio (95% confidence interval)	*P* value
	Present ($n = 469$)	Absent ($n = 6241$)			
Age (years)			0.265		
≤55	243 (51.8)	3067 (49.1)		1 (reference)	
>55	226 (48.2)	3174 (50.9)		0.729 (0.585–0.908)	0.005
Gender (%)			<0.001		
Male	248 (52.9)	3928 (62.9)		1 (reference)	
Female	221 (47.1)	2313 (37.1)		1.472 (1.186–1.825)	<0.001
Tumor site (%)			0.177		
Upper third	42 (9.0)	666 (10.7)		1 (reference)	
Middle third	131 (27.9)	1901 (30.5)		1.170 (0.787–1.739)	0.439
Lower third	296 (63.1)	3674 (58.9)		1.592 (1.099–2.306)	0.014
Macroscopic type (%)			0.059		
Elevated	62 (13.2)	651 (10.4)		1 (reference)	
Flat/depressed	407 (86.8)	5590 (89.6)		0.940 (0.675–1.309)	0.713
Ulcer (%)			0.154		
Absent	448 (95.5)	6038 (96.7)		1 (reference)	
Present	21 (4.5)	203 (3.3)		1.198 (0.711–2.016)	0.497
Tumor size (cm)			<0.001		
≤2.0	104 (22.2)	2606 (41.8)		1 (reference)	
2.1–3.0	76 (16.2)	1541 (24.7)		0.899 (0.650–1.243)	0.518
>3.0	289 (61.6)	2094 (33.6)		2.101 (1.630–2.709)	<0.001
Tumor depth (%)			<0.001		
Mucosa	128 (27.3)	4281 (68.6)		1 (reference)	
SM1	64 (13.6)	672 (10.8)		2.125 (1.508–2.995)	<0.001
SM2	122 (26.0)	645 (10.3)		3.392 (2.514–4.577)	<0.001
SM3	155 (33.0)	643 (10.3)		3.315 (2.453–4.480)	<0.001
Histological type (%)			<0.001		
Papillary adenocarcinoma	7 (1.5)	123 (2.0)		1 (reference)	
WD or MD adenocarcinoma	142 (30.3)	2569 (41.2)		1.784 (0.767–4.150)	0.179
PD adenocarcinoma or SRC carcinoma	320 (68.2)	3549 (56.9)		3.558 (1.521–8.326)	0.003
Lymphatic invasion (%)			<0.001		
Absent	216 (46.1)	5706 (91.4)		1 (reference)	
Present	253 (53.9)	535 (8.6)		7.220 (5.682–9.174)	<0.001
Venous invasion (%)			<0.001		
Absent	450 (95.9)	6189 (99.2)		1 (reference)	
Present	19 (4.1)	52 (0.8)		1.645 (0.889–3.046)	0.113
Perineural invasion (%)			<0.001		
Absent	442 (94.2)	6153 (98.6)		1 (reference)	
Present	27 (5.8)	88 (1.4)		1.148 (0.684–1.927)	0.602

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *SRC* signet ring cell

presence of a papillary component was not an independent risk factor for LN metastasis. Based on these results, they argued that it is unnecessary to change the endoscopic resection criteria for EGC with a papillary component from the current treatment guidelines. Lee et al. [6] compared clinicopathological features of patients with papillary EGC with those in WD or MD EGC and PD, SRC, or mucinous EGC, respectively. Papillary adenocarcinoma is defined as a tumor in which more than 50% of the tumor area contains papillary structures, as in our study. In univariate analysis, they found that the lymphovascular invasion rate in papillary EGC was significantly higher compared to that in nonpapillary EGC.

Table 4 Univariate analysis of clinicopathological characteristics associated with lymph node metastasis in early gastric papillary adenocarcinoma

Characteristic	Lymph node metastasis		*P* value
	Present ($n = 7$)	Absent ($n = 123$)	
Age (years)			0.348
≤55	0 (0.0)	24 (19.5)	
>55	7 (100.0)	99 (80.5)	
Gender (%)			1.000
Male	5 (71.4)	89 (72.4)	
Female	2 (28.6)	34 (27.6)	
Tumor site (%)			0.703
Upper third	0 (0.0)	10 (8.1)	
Middle third	1 (14.3)	21 (17.1)	
Lower third	6 (85.7)	92 (74.8)	
Macroscopic type (%)			0.053
Elevated	6 (85.7)	56 (45.5)	
Flat/depressed	1 (14.3)	67 (54.5)	
Ulcer (%)			1.000
Absent	7 (100.0)	120 (97.6)	
Present	0 (0.0)	3 (2.4)	
Tumor size (cm)			0.015
≤2.0	0 (0.0)	28 (22.8)	
2.1–3.0	0 (0.0)	41 (33.3)	
>3.0	7 (100.0)	54 (43.9)	
Tumor depth (%)			0.025
Mucosa	1 (14.3)	65 (52.8)	
SM1	0 (0.0)	19 (15.4)	
SM2	4 (57.1)	21 (17.1)	
SM3	2 (28.6)	18 (14.6)	
Lymphatic invasion (%)			0.013
Absent	2 (28.6)	94 (76.4)	
Present	5 (71.4)	29 (23.6)	
Venous invasion (%)			0.437
Absent	6 (85.7)	114 (92.7)	
Present	1 (14.3)	9 (7.3)	
Perineural invasion (%)			1.000
Absent	7 (100.0)	120 (97.6)	
Present	0 (0.0)	3 (2.4)	

The LN metastasis rate in papillary EGC was also higher than that in nonpapillary EGC, but the difference did not reach statistical significance. Multivariate analysis to identify independent predictive factors for LN metastasis was not performed with the whole study population in their study. When analyzing 56 patients with papillary EGC, lymphatic invasion was the only predictive factor for LN metastasis.

In the present study, both lymphatic invasion and venous invasion rates were the highest in papillary EGC compared to WD or MD EGC and PD or SRC EGC. As lymphovascular invasion is a well-known important risk factor for LN metastasis, it is expected that the LN metastasis rate would be higher in papillary EGC than in other subtypes of EGC. In the present study, however, LN metastasis rate in papillary EGC was comparable or lower than that in WD or MD EGC or PD or SRC EGC in both mucosal and submucosal cancers (1.5%, 1.1%, and 4.0% for mucosal EGCs and 9.45%, 11.9%, and 17.6% for submucosal EGCs, respectively). This mismatch might be explained by the low LN metastasis rates observed in papillary EGC with lymphatic or venous invasion. In the present study, LN metastasis rates in tumors with lymphatic or venous invasion were the lowest in patients with papillary EGC (14.7% and 10.0% in tumors with lymphatic and venous invasion, respectively). Our group previously investigated EGCs with lymphatic invasion and reported that LN metastasis rate was associated with lymphatic invasion grade stratified based on the number of lymphatic tumor emboli in whole sections [19]. Therefore, there might be a difference in lymphatic invasion grade between papillary EGC and other subtypes of EGC with lymphatic invasion.

Nakashima et al. [14] reported that papillary gastric adenocarcinoma with low-grade nuclear atypia was associated with lower frequency of lymphatic or venous invasion and lower frequency of LN metastasis compared to tumors with high-grade nuclear atypia. In their study, 88.7% of papillary EGC was classified as tumor with low-grade nuclear atypia. In our study, however, only 39.0% of papillary EGC was diagnosed as tumor with low-grade nuclear atypia. There was no significant difference in lymphatic invasion and LN metastasis rates between papillary EGCs with low-grade nuclear atypia and high-grade nuclear atypia. Further large studies are necessary to evaluate the role of nuclear atypia grading as a predictor for aggressive tumor features in papillary gastric adenocarcinoma.

In the present study, 57 mucosal papillary EGCs and 6 submucosal papillary EGCs met the curative endoscopic resection criteria, and none of these tumors showed LN metastasis in the surgical specimen. All 7 papillary EGCs with LN metastasis were beyond curative endoscopic resection criteria. In the study by Sekiguchi et al. [7], 4 EGCs with a papillary component in more than 50% of the tumor area showed LN metastasis. All these papillary EGCs had lymphatic invasion and were thus beyond curative endoscopic resection criteria. Consistent with these surgical data, there have been no studies that reported extragastric recurrence after curative endoscopic resection for papillary EGC [15–18].

This study was limited in that it was performed at a single tertiary referral center and had a retrospective design. Second, despite detailed pathology review on nuclear atypia grade and undifferentiated component in papillary EGCs, we could not clearly identify the mechanism underlying the

Table 5 Clinicopathological characteristics of patients with early gastric papillary adenocarcinoma with lymph node metastasis

Case number	Age (years)	Gender	Tumor site	Macroscopic type	Case	Tumor size (cm)	Tumor depth	Lymphatic invasion	Venous invasion	Perineural invasion
Case 1	79	F	Lower	Elevated	Neg	5.5	Mucosa	Pos	Neg	Neg
Case 2	56	M	Lower	Elevated	Neg	4.2	SM2	Pos	Neg	Neg
Case 3	81	M	Lower	Elevated	Neg	4.2	SM2	Pos	Neg	Neg
Case 4	69	M	Lower	Elevated	Neg	4.5	SM2	Neg	Neg	Neg
Case 5	64	F	Middle	Elevated	Neg	7.0	SM2	Pos	Neg	Neg
Case 6	67	M	Lower	Elevated	Neg	3.5	SM3	Neg	Neg	Neg
Case 7	60	M	Lower	Flat/depressed	Neg	3.8	SM3	Pos	Pos	Neg

F female, *M* male, *Pos* positive, *Neg* negative

Table 6 Lymphatic invasion and lymph node metastasis rates according to nuclear atypia grade in early gastric papillary adenocarcinoma

Rate	Low-grade nuclear atypia ($n = 46$)		High-grade nuclear atypia ($n = 72$)		*P* value
Lymphatic invasion (%)					0.293
Absent	36 (78.3)		50 (69.4)		
Present	10 (21.7)		22 (30.6)		
Lymph node metastasis (%)					1.000
Absent	43 (93.5)		68 (94.4)		
Present	3 (6.5)		4 (5.6)		
Rate	Lymphatic invasion (−) ($n = 36$)	Lymphatic invasion (+) ($n = 10$)	Lymphatic invasion (−) ($n = 50$)	Lymphatic invasion (+) ($n = 22$)	
Lymph node metastasis (%)					
Absent	35 (97.2)	8 (80.0)	49 (98.0)	19 (86.4)	
Present	1 (2.8)	2 (20.0)	1 (2.0)	3 (13.6)	

mismatch between aggressive feature of papillary EGC (high lymphatic invasion, venous invasion, and submucosal invasion rates) and comparable or lower LN metastasis rate in papillary EGC than in other subtypes of EGC.

In conclusion, we found that the LN metastasis rate in papillary EGC was comparable or lower than that in WD or MD EGC or PD or SRC EGC despite its higher lymphovascular invasion rate. Given no LN metastasis in papillary EGC that met the curative endoscopic resection criteria, endoscopic resection can be indicated for papillary EGC according to current guidelines [4]. Careful histological evaluation is required after endoscopic resection for papillary EGC because papillary EGC shows a considerable rate of lymphovascular invasion.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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