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ORIGINAL ARTICLE

Clinical application of early gastric carcinoma with lymphoid stroma based on lymph node metastasis status

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Abstract

Background Gastric carcinoma with lymphoid stroma (GCLS) is characterized by undifferentiated carcinoma mixed with prominent lymphoid infiltration. GCLS has unique clinicopathological features and a better prognosis compared to other types of gastric cancer. We analyzed the clinicopathological features of early GCLS in relation to lymph node metastasis (LNM).

Methods We performed a retrospective analysis of 241 patients diagnosed with GCLS confined to the mucosa or the submucosa between March 1998 and December 2015. Their data were compared with those from 1219 patients who underwent resection for differentiated early gastric cancer (EGC).

Results Of the 241 patients analyzed, 33 (13.7%) had intramucosal cancers and 208 (86.3%) had cancers that penetrated the submucosa. Compared to differentiated EGC, early GCLS was more prevalent in younger individuals and in men, tended to be proximally located, was highly associated with Epstein–Barr virus (EBV) infection (89.2%), and had a lower risk of LNM. The 5-year disease-specific survival rate of patients with early GCLS was 98.3% but depended significantly on LNM status ($p < 0.001$) and EBV infection status ($p = 0.039$). The risk of LNM from mucosal GCLS and submucosal GCLS was 0% [95% confidence interval (CI) 0–9.1] and 10% (95% CI 6.8–15.2), respectively. On multivariate analysis, LNM was found to be associated with tumor size ($p = 0.022$) and lymphovascular invasion ($p = 0.002$) in addition to tumor depth.

Conclusions Early GCLS has distinct clinicopathological features depending on age, sex, tumor location, EBV infection status, and LNM status. Tailored therapies, including endoscopic treatment, are needed based on the distinct clinicopathological features of early GCLS.

Keywords Epstein–Barr virus · Stomach · Early gastric cancer · Gastric carcinoma with lymphoid stroma

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Introduction

Despite decreasing in incidence throughout the twentieth century, gastric cancer remains the fourth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide [1, 2]. Gastric cancer is clinically classified as early (cancer that is limited to the mucosa or submucosa) or advanced (cancer that has invaded the deeper gastric wall) stage disease to help determine the appropriate intervention, and it is histologically classified into several subtypes based on its major morphologic components [3–5]. Previous studies demonstrated that

gastric cancer has different clinicopathological features and prognoses depending on its clinical or histological subtypes, and the survival of early gastric cancer (EGC) patients following surgical or endoscopic resection is excellent (5-year survival rate: 70–95%) [3]. In addition, recent molecular analyses have demonstrated the presence of molecular heterogeneity through the existence of subtypes, although there is a lack of consensus among researchers in the field regarding this information [6].

Gastric carcinoma with lymphoid stroma (GCLS), which also is known as gastric lymphoepithelioma-like carcinoma, is a histological subtype of gastric cancer that is characterized by undifferentiated carcinoma mixed with prominent lymphoid infiltration [7]. The incidence of GCLS is 1–4% of all gastric cancer cases, and more than 80% of GCLS cases are associated with Epstein–Barr virus (EBV) infection [8–10]. There have been some reports that GCLS has distinctive clinicopathological features and is associated with a significantly better prognosis compared to other subtypes [11, 12]. However, data on GCLS are insufficient owing to its rarity, and there are only a few studies on the clinicopathological features of early GCLS [7].

This study aimed to analyze the clinicopathological features of early GCLS and to compare them with those of conventional differentiated gastric adenocarcinoma. Based on this analysis, we intended to identify risk factors of lymph node metastasis (LNM) in early GCLS and to explore whether local resection including endoscopic resection might be eligible in the treatment of those tumors.

Methods

Study population

Between March 1998 and December 2015, 481 patients who were pathologically diagnosed with GCLS underwent surgical resection at our institution. Of these patients, we retrospectively reviewed patients who met the following inclusion criteria: (1) pathologically confirmed GCLS that is confined to either the mucosa or the submucosa; (2) complete clinical information available for further analysis, including treatment history and outcomes; and (3) gastric cancer tissue specimens available for EBV analysis. A total of 241 patients who met the inclusion criteria were enrolled in the study, 113 of whom were subjects in our previous study [11]. To compare these cases with conventional gastric adenocarcinomas (with no GCLS morphology), 1219 patients who underwent surgical resection for differentiated EGC between January 2008 and December 2011 were evaluated. This study was approved by the institutional review board of Asan Medical Center.

Clinicopathological data

Clinical data, including age, sex, and treatment outcomes, were obtained through medical chart reviews and telephone interviews. Histopathological data, including macroscopic type, tumor location, tumor size, tumor depth, LNM, lymphovascular invasion, and perineural invasion, were collected after reviewing histology slides and pathology reports. In cases of GCLS, the presence of EBV in the cancer cells was additionally assessed via EBV-encoded RNA chromogenic in situ hybridization.

GCLS was defined according to the 2010 World Health Organization (WHO) classification guidelines as a poorly or undifferentiated tumor with prominent lymphoid infiltration [3]. The Paris classification was used to categorize the macroscopic type of early GCLS [13]; type 1 (protruded) and type 2a (superficial elevated) were categorized as the elevated type, type 2b (flat) as the flat type, and type 2c (superficial depressed) and type 3 (excavated) as the depressed type. The degree of submucosal penetration was classified into three groups: SM1 (penetration up to one-third of the submucosal layer), SM2 (penetration up to two-thirds of the submucosal layer), and SM3 (penetration of greater than two-thirds of the submucosal layer). Patients with multiple tumors were staged according to the deepest-penetrating tumor. All histological slides were reviewed by two experienced gastrointestinal pathologists (YSP and HJK).

EBV-encoded RNA chromogenic in situ hybridization

The presence of EBV in the cancer cells was assessed according to the protocol described in our previous study for EBV chromogenic in situ hybridization using an automatic staining device (Benchmark XT, Ventana, Tucson, AZ, USA) [11]. Briefly, 4-μm-thick sections were cut from representative blocks obtained from each patient, mounted onto coated slides, and dried at 74 °C for 30 min. After pretreatment with ISH protease 2 (Ventana) for 8 min at 37 °C, the slides were denatured at 85 °C for 12 min and hybridization was conducted at 57 °C for 1 h using EBV-encoded small RNA probes (INFORM, Ventana) that had been labeled with fluorescein. Detection was sequentially performed by applying mouse anti-fluorescein antibody and biotinylated goat anti-mouse antibody (iView blue; Ventana); counterstaining was performed using nuclear fast red. Strong staining in the nucleus was considered to indicate positivity, and the proportion of EBV-positive tumor cells was thereby evaluated.

Statistical analyses

The chi-square test was used to test for associations among various categorical variables, and the independent-samples

t test was used for noncategorical variables. Multivariate logistic regression analysis was used to assess the risk factors for LNM. Disease-specific overall survival (OS), defined as the time from the date of diagnosis to the date of death, was calculated using the Kaplan–Meier method. Survival was compared using the log-rank test. Statistical analyses were performed using SPSS software (version 22.0; SPSS, Chicago, IL, USA), and $p < 0.05$ was considered statistically significant.

Results

Clinicopathological features of early gastric carcinoma with lymphoid stroma

Of the 241 patients analyzed, the mean age was 58.8 years (range 31–80 years), and 205 (85.1%) were men. Curative gastrectomy with extended lymphadenectomy was performed on all patients. Thirty-three (13.7%) tumors were intramucosal cancers, and 208 (86.3%) penetrated the submucosa.

Table 1 shows the clinicopathological features of patients with early GCLS and the control group. Compared with the control group, early GCLS was more common in men ($p = 0.023$) and in younger individuals ($p = 0.003$), and they more frequently presented the protruded macroscopic type ($p = 0.019$), ulceration ($p < 0.001$), and proximal locations ($p < 0.001$). Although submucosal invasion was more common in patients with early GCLS ($p < 0.001$), there was no significant difference in the tumor size ($p = 0.073$), rates of LNM ($p = 0.498$), and perineural invasion ($p = 0.207$) between the two groups. In contrast, lymphovascular invasion ($p = 0.042$) was more prevalent in the control group.

Clinicopathological features of early gastric carcinoma with lymphoid stroma according to tumor depth

Compared to the control group with mucosal invasion, patients with mucosal GCLS showed similar clinicopathological features with the exception of the tumor location (Table 2). Patients with mucosal GCLS more frequently presented a proximal tumor location than the patients in the control group did ($p < 0.001$).

Table 3 shows the clinicopathological characteristics of patients with submucosal GCLS and those of the control group with submucosal invasion. Patients with submucosal GCLS were younger ($p < 0.001$), and showed more ulceration ($p = 0.001$), proximal locations ($p < 0.001$), and smaller tumor sizes ($p = 0.012$) than the control group. In addition,

Table 1 Comparison of patient characteristics between the early GCLS and control groups

Factor	GCLS ($n = 241$)	Control ($n = 1219$)	p value
Age, mean (years, range)	58.8 (31–80)	60.9 (29–85)	0.003
Sex, male (%)	205 (85.1)	958 (78.6)	0.023
Macroscopic type (%)			0.019
Protruded	85 (35.3)	345 (28.4)	
Flat	36 (14.9)	266 (21.9)	
Depressed	120 (49.8)	605 (49.7)	
Ulceration (%)	27 (11.2)	50 (4.12)	<0.001
Location of tumor (%)			<0.001
Upper third	78 (32.4)	149 (12.2)	
Middle third	119 (49.4)	189 (15.5)	
Lower third	44 (18.2)	881 (72.3)	
Number of tumors (%)			0.751
Single	212 (88.0)	1081 (88.7)	
Multiple	29 (12.0)	138 (11.3)	
Tumor size, mean (cm, range)	3.03 (0.3–13.6)	3.24 (0.1–14.0)	0.073
Depth of tumor (%)			<0.001
Mucosal invasion	33 (13.7)	522 (42.8)	
Submucosal invasion	208 (86.3)	697 (57.2)	
Lymph node metastasis[a] (%)	22 (9.1)	129 (10.6)	0.498
Lymphovascular invasion (%)	27 (11.2)	200 (16.4)	0.042
Perineural invasion (%)	5 (2.1)	45 (3.7)	0.207

GCLS gastric carcinoma with lymphoid stroma

[a] 95% confidence interval (CI) of the GCLS group, 5.35–12.65; 95% CI of the control group, 8.98–12.44

Table 2 Comparison of patient characteristics between the mucosal GCLS and control groups

Factor	GCLS ($n = 33$)	Control ($n = 522$)	p value
Age, mean (years, range)	61.2 (46–78)	59.7 (29–82)	0.353
Sex, male (%)	27 (81.8)	397 (76.1)	0.449
Macroscopic type (%)			0.111
Protruded	5 (15.2)	110 (21.1)	
Flat	5 (15.2)	145 (27.8)	
Depressed	23 (69.6)	267 (51.1)	
Ulceration (%)	3 (9.1)	14 (2.7)	0.074
Location of tumor (%)			<0.001
Upper third	9 (27.3)	49 (9.4)	
Middle third	17 (51.5)	85 (16.3)	
Lower third	7 (21.2)	388 (74.3)	
Number of tumors (%)			0.999
Single	29 (87.9)	450 (86.2)	
Multiple	4 (12.1)	72 (13.8)	
Tumor size, mean (cm, range)	2.33 (0.3–5.5)	2.90 (0.1–10.0)	0.092
Depth of tumor (%)			0.249
Lamina propria	18 (54.5)	231 (44.3)	
Muscularis mucosa	15 (45.5)	291 (55.7)	
Lymph node metastasis[a] (%)	0 (0)	5 (0.96)	0.999
Lymphovascular invasion (%)	1 (3.0)	12 (2.3)	0.553
Perineural invasion (%)	1 (3.0)	0 (0)	0.059

GCLS gastric carcinoma with lymphoid stroma

[a] 95% confidence interval (CI) of the GCLS group, 0–9.09; 95% CI of the control group, 0.40–2.28

despite having deeper submucosal invasion ($p < 0.001$), the submucosal GCLS group showed less frequent LNM ($p = 0.013$), lymphovascular invasion ($p < 0.001$), and perineural invasion ($p = 0.008$) than the control group.

Clinicopathological features of early gastric carcinoma with lymphoid stroma according to EBV infection status

Among the 241 patients analyzed, a total of 215 patients (89.2%) showed EBV positivity. The clinicopathological features of patients with EBV-positive and EBV-negative early GCLS are described in Table 4. EBV-positive early GCLS was associated more frequently with younger individuals ($p = 0.004$), men ($p = 0.017$), and a proximal tumor location ($p < 0.001$) compared to EBV-negative early GCLS. Although there was no significant difference in tumor depth between the two groups ($p = 0.447$), LNM ($p = 0.058$) and lymphovascular invasion ($p = 0.042$) were more prevalent in EBV-negative early GCLS.

Lymph node metastasis of early gastric carcinoma with lymphoid stroma

The overall risk of LNM of early GCLS (22 of 241 patients) was 9.1% [95% confidence interval (CI) 5.4–12.7]; the risk of LNM of mucosal GCLS (0 of 33 patients) was 0% (95% CI 0–9.1), and the risk of LNM of submucosal GCLS (22 of 208 patients) was 10.6% (95% CI 6.8–15.2). LNM was not observed in 72 patients with early GCLS invading the mucosal or SM1-2 layer, regardless of the tumor size (Fig. 1). A multivariate analysis that included variables which were significant in the univariate analysis indicated that tumor size ($p = 0.022$) and lymphovascular invasion ($p = 0.002$) were significantly associated with LNM (Table 5). Although EBV-positive early GCLS showed a decreased risk of LNM in the univariate analysis, this did not reach statistical significance (see Table S1 in the Electronic supplementary material, ESM). The depth of tumor could not be evaluated in the univariate and multivariate analyses because none of the patients with mucosal and SM1-2 invasion showed LNM.

Survival of early GCLS

With a median follow-up period of 31.5 months (range 2–171 months), the 5-year disease-specific survival rate of early GCLS was 98.3%, and disease-related death occurred in just two cases with deep submucosal invasion (SM3) and LNM. Two cases with disease-related death showed recurrences at abdominal lymph nodes and the peritoneum 23 and 25 months after curative gastrectomy, respectively.

Table 3 Comparison of patient characteristics between the submucosal GCLS and control groups

Factor	GCLS ($n = 208$)	Control ($n = 697$)	p value
Age, mean (years, range)	58.4 (31–80)	61.8 (30–85)	<0.001
Sex, male (%)	178 (85.6)	561 (80.5)	0.096
Macroscopic type (%)			0.423
Protruded	80 (38.5)	236 (33.9)	
Flat	31 (14.9)	122 (17.4)	
Depressed	97 (46.6)	339 (48.7)	
Ulceration (%)	24 (11.5)	36 (5.2)	0.001
Location of tumor (%)			<0.001
Upper third	69 (33.2)	100 (14.4)	
Middle third	102 (49.0)	104 (14.9)	
Lower third	37 (17.8)	493 (70.7)	
Number of tumors (%)			0.283
Single	183 (87.9)	631 (90.5)	
Multiple	25 (12.1)	66 (9.5)	
Tumor size, mean (cm, range)	3.14 (0.5–13.6)	3.51 (0.6–14.0)	0.012
Depth of tumor (%)			<0.001
SM1 invasion	14 (6.7)	157 (22.5)	
SM2–3 invasion	194 (93.3)	540 (77.5)	
Lymph node metastasis[a] (%)	22 (10.6)	124 (17.8)	0.013
Lymphovascular invasion (%)	26 (12.5)	118 (26.9)	<0.001
Perineural invasion (%)	4 (1.9)	45 (6.5)	0.008

GCLS gastric carcinoma with lymphoid stroma, *SM1* penetration up to 1/3 of the submucosal layer, *SM2* penetration up to 2/3 of the submucosal layer, *SM3* penetration greater than 2/3 of the submucosal layer

[a] 95% confidence interval (CI) of GCLS group, 6.81–15.19; 95% CI of control group, 15.13–20.81

Figure 2 shows disease-specific survival curves for the early GCLS and control groups according to LNM status and EBV infection status. Although there was no significant difference between the early GCLS and control groups, early GCLS showed a significant difference in prognosis according to LNM status (5-year disease-specific survival rate, 100 vs. 86.2%, respectively) ($p < 0.001$) (Fig. 2a). Figure 2b shows disease-specific survival curves for early GCLS according to EBV infection status. EBV-positive GCLS was associated with a better prognosis than EBV-negative GCLS (5-year disease-specific survival rate, 99.1 vs. 90.0%, respectively) ($p = 0.039$).

Discussion

GCLS has unique clinicopathological features and a better prognosis than other subtypes of gastric cancer. However, it is not known whether early GCLS has a similar prognosis and clinicopathological features to GCLS. In this study, early GCLS showed clinicopathological features distinct from those of conventional gastric adenocarcinomas (with no GCLS morphology) in terms of age, sex, ulceration, tumor location, tumor size, lymphovascular invasion, perineural invasion, and LNM. Early GCLS also showed different clinicopathological features and prognoses according to EBV infection status.

GCLS frequently affects the proximal stomach or gastric stump and is more common in men and younger individuals [14, 15]. In addition, ulcerated or subepithelial tumor-like protrusions are often considered to be characteristic endoscopic findings of GCLS [15, 16]. In this study, compared with differentiated EGC, early GCLS was prevalent in younger individuals and men, tended to be proximally located, and was more frequently ulcerated. These findings are consistent with the results of previous studies [14, 15]. However, unlike that observed in previous studies, the predominant macroscopic type of early GCLS was the depressed type, which was not significantly different from tumor depth-matched differentiated EGC [15, 16]. The disparity in the macroscopic type between these studies may result from the different enrollment criteria employed in the current study—we only analyzed patients with early GCLS.

It is thought that EBV infection may play a key role in the pathogenesis of GCLS, although the mechanism for this is still not known. We have demonstrated that GCLS shows a different prognosis and clinicopathological features

Table 4 Clinicopathological features of early GCLS according to EBV infection status

Factor	EBV-positive ($n = 215$)	EBV-negative ($n = 26$)	p value
Age, mean (years, range)	58.2 (31–79)	64.1 (43–80)	0.004
Sex, male (%)	187 (86.9)	18 (69.2)	0.017
Macroscopic type (%)			0.488
Protruded	74 (34.4)	11 (42.3)	
Flat	34 (15.8)	2 (7.7)	
Depressed	107 (49.8)	13 (50)	
Ulceration (%)	23 (10.7)	4 (15.4)	0.507
Location of tumor (%)			<0.001
Upper third	74 (34.4)	4 (15.4)	
Middle third	116 (54.0)	3 (11.5)	
Lower third	25 (11.6)	19 (73.1)	
Number of tumors (%)			0.333
Single	187 (86.9)	25 (96.2)	
Multiple	28 (13.1)	1 (3.8)	
Tumor size, mean (cm, range)	2.99 (0.2–13.6)	3.32 (0.6–7.3)	0.359
Depth of tumor (%)			0.447
Lamina propria	18 (8.4)	0 (0)	
Muscularis mucosa	14 (6.5)	1 (3.8)	
SM1 invasion	13 (6.0)	1 (3.8)	
SM2–3 invasion	170 (79.1)	24 (92.4)	
Lymph node metastasis (%)	17 (7.9)	5 (19.2)	0.058
Lymphovascular invasion (%)	21 (9.8)	6 (23.1)	0.042
Perineural invasion (%)	4 (1.9)	1 (3.8)	0.438

EBV Epstein–Barr virus, *GCLS* gastric carcinoma with lymphoid stroma, *SM1* penetration up to 1/3 of the submucosal layer, *SM2* penetration up to 2/3 of the submucosal layer, *SM3* penetration greater than 2/3 of the submucosal layer

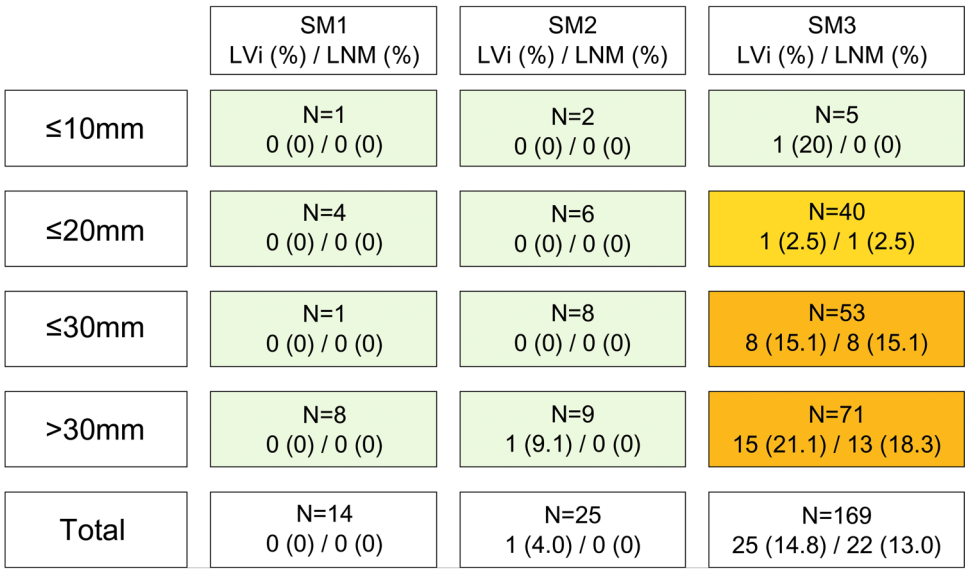

Fig. 1 Lymph node metastasis and lymphovascular invasion by submucosal gastric carcinoma with lymphoid stroma

depending on the EBV infection status [11]. According to our results, early GCLS is highly associated with EBV infection (89.2%), and it shows different clinicopathological features and prognoses depending on EBV infection status. EBV-positive early GCLS was more strongly associated with younger age, male sex, proximal location, lower LNM, lymphovascular invasion, and a favorable prognosis compared to EBV-negative early GCLS,

Table 5 Multivariate association with lymph node metastasis in patients with early GCLS

	Odds ratio	95% CI (lower–upper)	*p* value
Tumor size, 1 cm increase	1.309	1.039–1.648	0.022
Lymphovascular invasion	4.920	1.762–13.736	0.002

GCLS gastric carcinoma with lymphoid stroma, *CI* confidence interval, *EBV* Epstein–Barr virus

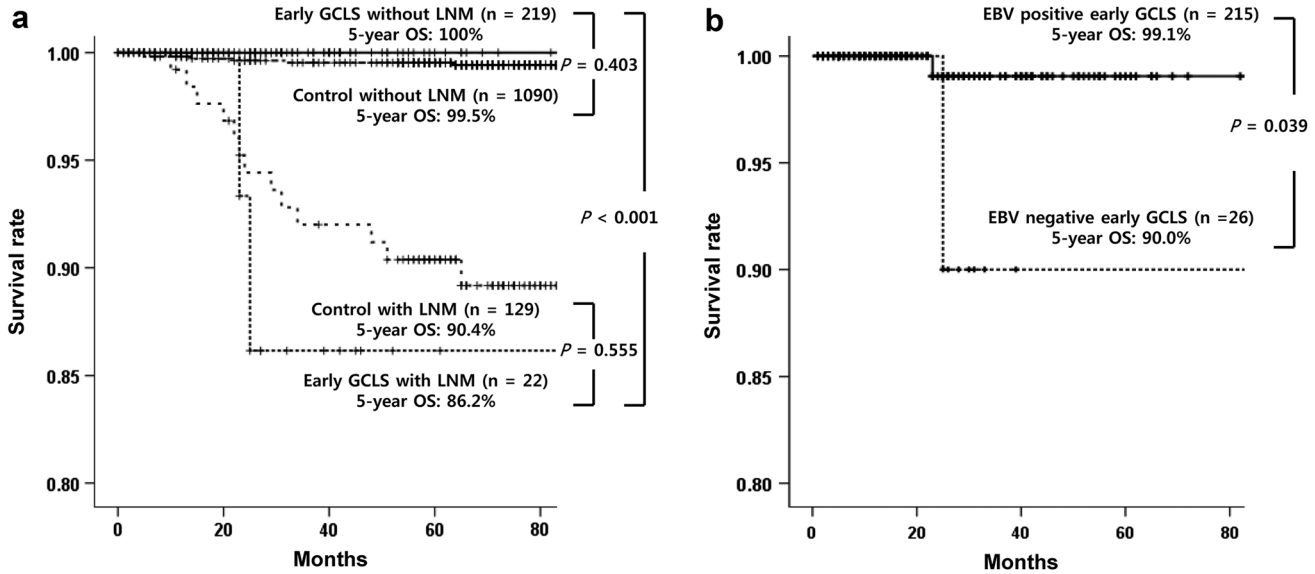

Fig. 2a–b Kaplan–Meier estimation of disease-specific survival curves. **a** Disease-specific survival of patients with early gastric carcinoma with lymphoid stroma according to lymph node metastasis status. **b** Disease-specific survival of patients with early gastric carcinoma with lymphoid stroma according to Epstein–Barr virus infection status

although the difference in LNM did not reach statistical significance ($p = 0.058$). These findings are consistent with those of our previous study, and they support our opinion that EBV assessments should be performed to predict the prognosis in patients with GCLS, including early GCLS [11].

Endoscopic resection has been accepted as a curative local treatment for EGC with a low likelihood of LNM [4, 5]. However, histologically undifferentiated EGC tends to have LNM more often than differentiated EGC does, and it is considered to be unsuitable for endoscopic resection [17, 18]. It is known that GCLS has a lower risk of LNM than other subtypes of gastric cancer [14]. Also, in a recent study of ezrin targeting, it was found that ezrin expression is correlated with EBV-positive GCLS, and that the phosphorylation of ezrin is essential in the LNM of GCLS [19]. However, despite its low risk of LNM, GCLS can be classified as undifferentiated cancer due to its undifferentiated histological features and indistinct histological classification. Furthermore, there have been no previous studies regarding the exact incidence of LNM of early GCLS. In this study, the risk of LNM of early GCLS was 9.1% (95% CI 5.4–12.7). The risks of LNM of mucosal GCLS and LNM of submucosal GCLS were 0% (95% CI 0–9.1) and 10.6% (95% CI 6.8–15.2), respectively. Although the risk of LNM was not significantly different between GCLS and the differentiated EGC that was confined to the mucosa, the risk of LNM of submucosal GCLS was significantly lower than that of the controls with submucosal invasion. Furthermore, LNM was only observed in patients with SM3 invasion. Compared with previous studies that evaluated the risk of LNM of EGC, early GCLS has at least an equal or lower risk of LNM compared to differentiated EGC [17, 18]. GCLS is frequently located in the proximal portion of the stomach, and it usually requires total or near-total gastrectomy for surgical treatment in current clinical practice. Although there are some limitations of applying endoscopic resection for early GCLS (it is often accompanied by ulceration, and most GCLSs invade into the submucosa, making it difficult to estimate the depth of invasion), our results suggest that local resection such as endoscopic resection and cooperative endoscopic laparoscopic surgery could be an important treatment option for patients with early GCLS.

Predicting LNM is helpful when deciding the treatment plan for EGC. Many studies have tried to predict LNM by analyzing various clinicopathological factors and imaging modalities [17, 20–22]. However, the available imaging

methods for the preoperative detection of LNM are not sufficiently accurate. The diagnostic accuracies of endoscopic ultrasonography and computed tomography are 50–87 and 52–71%, respectively [20, 22]. Therefore, it is important to determine the clinicopathological factors associated with LNM in patients with EGC. In the present study, multivariate analysis demonstrated that the presence of lymphovascular invasion and tumor size are independent predictive factors for LNM of early GCLS in addition to tumor depth, although tumor depth could not be evaluated for statistical reasons. These results are in agreement with those of previous studies reporting that lymphovascular invasion, tumor size, and tumor depth are associated with LNM of conventional EGC [17, 18]. Our findings determined the predictive factors that can be used to identify patients with early GCLS who are at a high risk for LNM and who should be offered gastrectomy rather than endoscopic resection. In addition, if the histological assessment shows a low risk for LNM, patients with early GCLS who underwent endoscopic resection can be carefully observed without additional surgical treatment; this is especially important for patients with comorbidities and those for whom surgery would be risky.

GCLS has been associated with a survival advantage compared with conventional gastric adenocarcinoma (with no GCLS morphology) [11, 23]. Lymphocytic infiltration around the tumor is considered a host immune reaction against the tumor cells [24]. A recent study demonstrated an association between expression of programmed death ligand 1 (PD-L1) and lymphocytic infiltration in EBV-associated gastric cancer, although the exact role of PD-L1 remains uncertain [25]. In this study, despite deeper submucosal invasion, early GCLS was associated with a smaller tumor size and lower levels of lymphovascular invasion, perineural invasion, and LNM compared with differentiated EGC. These findings may be associated with the antitumor effect of immunity caused by lymphocytic infiltration. However, contrary to these findings, there was no significant difference in 5-year disease-specific survival rate between early GCLS and differentiated EGC, although patients with early GCLS had excellent prognoses (mean 5-year disease-specific survival rate: 98.3%). This finding is consistent with that observed in our previous study, which determined that there was no significant difference in prognosis between early stage GCLS (American Joint Committee on Cancer stages I and II) and conventional gastric cancer [11]. Previous studies have demonstrated that EGC has an excellent prognosis irrespective of histological type, level of submucosal infiltration, LNM status, and tumor size if curative resection is achieved [26, 27]. In early GCLS, curative resection is considered the most important factor affecting the prognosis of patients.

This study has several limitations. First, the analysis had a retrospective, nonrandomized design. This could have led to biases because of unrecognized or unmeasured factors. Second, because of the small sample size, the upper limit of the 95% CI calculated from this study was too large to exclude the possibility of LNM in patients with mucosal GCLS. Third, although we suggested that local resection could be a therapeutic option for early GCLS, we did not describe the therapeutic indications that can be applied when considering endoscopic resection. Also, the preoperative diagnostic yield using endoscopic forceps biopsy specimens was lower (5%) than that of differentiated EGC, although we did not show this in the present study. Further studies investigating the clinical indications for endoscopic resection and histological features of endoscopic forceps biopsy specimens are needed.

In conclusion, early GCLS has distinct clinicopathological features that are similar to those of GCLS (as identified in previous studies) in terms of age, sex, tumor location, LNM, and EBV infection status. In addition, early GCLS has different clinicopathological features and prognoses depending on EBV infection status. Early GCLS has an equal or lower risk of LNM compared to differentiated EGC, and local resection including endoscopic resection can be a useful treatment option for early GCLS. Further investigation of the pathological features and molecular mechanisms according to the specific subtypes of gastric cancer is necessary in order to develop more effective therapies for individuals with early GCLS.

Compliance with ethical standards

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

Research involving human participants and informed consent All procedures were conducted 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 or a substitute for it was obtained from all patients included in the study.

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