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Original contribution

Micropapillary early gastric carcinoma with distinct clinicopathological features, high risk for lymph node metastasis, and dismal prognosis: a multicenter clinicopathological study of 29 cases identified in 1890 early gastric carcinoma radical gastrectomies☆,☆☆

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Summary Clinicopathology and risk factors of lymph node metastasis (LNM) in micropapillary early (pT1) gastric carcinoma (MEGC) remain elusive because of the extreme rarity. In this multicenter study, we investigated 1890 consecutive radical resections of early gastric carcinoma diagnosed with the World Health Organization criteria and identified 29 (1.5%) MEGC cases with a small (≥5%) micropapillary component. MEGC showed a male predominance (male-to-female ratio, 21:8). Most (93.1%; 27/29) tumors invaded submucosa. Lymphovascular invasion was detected in 14 (48.3%) of 29 cases. LNM was found in 13 cases (44.8%; 11 identified with a routine hematoxylin-eosin stain and 2 additional cases with a positive pancytokeratin immunostain). Overall, independent risk factors for LNM in early gastric carcinoma included patient age of 62 years

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or less, female sex, noncardiac location, ulcerative pattern, tumor size of greater than 2 cm, submucosal invasion, Lauren diffuse type, lymphovascular invasion, and MEGC. In MEGC, advanced pathologic stages were demonstrated in 6 (20.7%) of 29 cases. The 5-year overall survival rate of MEGC patients was 58.6%. Submucosal invasion, lymphovascular invasion, and LNM were significantly more frequent in the MEGC group than in the non-MEGC groups. Advanced pathologic stages were significantly more common in MEGC than in nonmicropapillary Lauren intestinal- but not diffuse-type early gastric carcinomas. In conclusion, MEGC demonstrated a high propensity for lymphovascular invasion, LNM with advanced stages, and dismal prognosis.
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1. Introduction

According to the 2012 World Health Organization (WHO) statistical data, gastric cancer is the sixth most common cancer and ranks the fourth leading cause of cancer-related deaths [1], especially in China [2], Japan, and Korea [1]. At present, curative resection remains the only hope for long-term survival when gastric cancer is diagnosed and resected at the early (pT1) stage, also known as early gastric carcinoma. Because of reported negligible risk for lymph node metastasis (LNM) in early gastric carcinoma [3], especially for nonulcerative, small (<3 cm), Lauren intestinal-type tubular and papillary adenocarcinomas [4], endoscopic therapy, such as endoscopic submucosal dissection, has become the treatment of choice for early gastric carcinoma with advantages over open surgical resection in safety, effectiveness, extend of injury, and quality of life after resection [5].

We noted previously in single-center studies on early gastric carcinoma that some papillary early gastric carcinomas with a small (≥5%) micropapillary component showed a high (50%; 2/4) frequency of LNM. The significance of such a finding is unknown in early gastric carcinoma because of the rarity [6,7]. However, carcinoma with micropapillary features has been reported to have aggressive behavior such as lymphovascular invasion and LNM in the breast [8], lung [9], colorectum [10], urinary bladder [11], salivary gland [12], and also stomach [13]. For micropapillary gastric carcinoma, almost all published studies were carried out in carcinomas diagnosed at advanced stages [13-16], and clinicopathological features of micropapillary early gastric carcinoma (MEGC) stay elusive. However, it is critically important to illustrate clinicopathological features of MEGC for clinical decision making on an optimal patient management strategy when MEGC is detected in small biopsies.

The aim of the present multicenter study was to investigate and compare clinicopathological features of MEGC with those of non-MEGC with the Lauren intestinal- or diffuse-type histology [17], as well as prognosis of MEGC patients.

2. Materials and methods

2.1. Patient selection

Electronic pathology archives were searched for the diagnosis of gastric carcinoma in radical gastrectomy with lymph node dissection at 4 participating tertiary medical centers over the period of 11 years for the Nanjing Drum Tower Hospital and Changzhou Second People's Hospital, 5 years for the Jiangsu Provincial Hospital of Traditional Chinese Medicine, and 4 years for the First Affiliated Hospital of Soochow University. Each report was scrutinized for the final diagnosis of early gastric carcinoma (pT1) with the tumor invasion confined to mucosa or submucosa on the basis of the WHO definition [18]. Excluded were the cases with synchronous carcinoma, cases with gastric stump carcinoma, and cases without tumor blocks. In addition, cases with high-grade dysplasia or invasion into the muscularis propria were also eliminated (Fig. 1). Patient private identification information such as name, telephone number, and address, and so on, was deleted, and each case was indexed with a pathology accession number to protect patient privacy. The study protocol was approved by the medical ethics committee of the participating medical centers.

2.2. Study groups

All early gastric carcinoma cases were divided into either MEGC or non-MEGC groups on the basis of whether they were with or without a mixed small (≥5%) micropapillary carcinoma component. The MEGC group was subgrouped either as mixed papillary/poorly cohesive (including signet ring cell) carcinoma or as mixed tubular adenocarcinoma. Similarly, the non-MEGC group was further divided into either the Lauren intestinal type with tubular or papillary (including micropapillary) adenocarcinoma or the Lauren diffuse-type early gastric carcinoma including poorly differentiated adenocarcinoma, poorly cohesive carcinoma, and mucinous adenocarcinoma, adenosquamous carcinoma, and carcinoma with lymphoid stroma [18].

2.3. Pathology investigation

All surgical radical resection specimens were routinely processed with a standard surgical pathology protocol. The patient demographic and pathologic information on tumor location, size, shape, surface feature, and macroscopic pattern was abstracted from pathology reports. The stomach was divided into 5 regions: (1) cardia, defined as a proximal gastric region of approximately 3 cm below the gastroesophageal junction [6], (2) fundus, (3) corpus, (4) incisura angularis, and (5) antrum-pylorus. Tumor macroscopic patterns after formalin fixation were categorized into 5 groups in accordance with the WHO classification: (1) broad-based protruding (0-

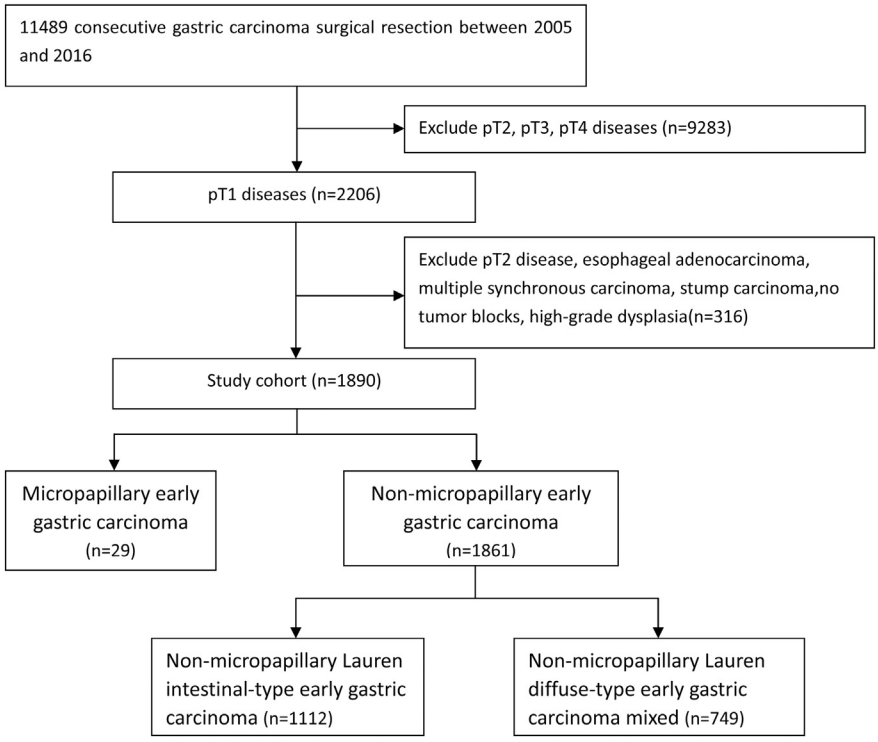

Fig. 1 Flowchart on selection of patients for this study.

I), (2) slightly elevated-rough (0-IIa), (3) flat (0-IIb), (4) superficially depressed (0-IIc), and (5) excavated (0-III) [18]. For early gastric carcinoma with more than 1 macroscopic patterns, the predominant (>50%) pattern was recorded.

All histology slides of each eligible early gastric carcinoma case were retrieved and reviewed for verification of early gastric carcinoma diagnosis and evaluation of pathologic features by at least 2 experienced study pathologists. The histopathologic diagnostic criteria for MEGC were defined as small clusters of tumor cells lacking true fibrovascular cores, surrounded by empty spaces, and involving at least 5% of the estimated total tumor volume on the same slide [6].

Tumor invasion depth was assessed microscopically and tabulated into 4 groups: (1) M2, intramucosal carcinoma without involvement of the muscularis mucosae; (2) M3, carcinoma involvement of the muscularis mucosae; (3) SM1, carcinoma invading into superficial submucosa (<0.5 mm from the muscularis mucosae); and (4) SM2, invading into deep submucosa (>0.5 mm from the muscularis mucosae). Also recorded were lymphovascular invasion, perineural invasion, and the numbers of total lymph nodes retrieved and involved. The eighth edition of the American Joint Committee on Cancer staging manual was followed for pathologic staging [19].

2.4. Immunohistochemical staining

Immunohistochemistry of pancytokeratin (AE1/AE3) was carried out on lymph nodes that were diagnosed as the absence of carcinoma metastasis on the basis of histopathologic evaluation of hematoxylin-eosin–stained slides in MEGC cases. Under a routine immunostaining protocol, paraffin-embedded, formalin-fixed tissue blocks were cut at 4-μm thickness, and tissue sections were immunostained with the Ventana Benchmark XT autostainer for AE1/AE3 (Dako, Carpentaria, CA). Appropriate positive and negative controls were included in each run.

2.5. Patient survival investigation

In 29 MEGC cases, patient survival investigation was carried out via telephone interview by study pathologists to patients or patient family members. The number of survival months after radical gastrectomy was calculated from the month of surgical resection to the month of the last interview or patient death of all causes.

2.6. Statistical analysis

Clinicopathological features, including patient age, sex, tumor location, size, macroscopic pattern, invasion depth, lymphovascular invasion, LNM, perineural invasion, pathologic stage, and survival, were collected, tabulated, and statistically analyzed. Differences between groups were determined using the χ^2 or Fisher exact test. Overall survival (OS) rates were evaluated using the Kaplan-Meier method. Risk factors for LNM were analyzed using the logistic regression method. Significant risk factors identified by univariate analysis were further analyzed using the multivariate model to assess independent risk factors for LNM. A P value of less than .05 was considered

statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 19.0 (IBM, Armonk, NY).

3. Results

3.1. Clinicopathological characteristics

Among 1890 (16.5%) eligible early gastric carcinoma cases identified from 11 489 radical gastrectomies for gastric cancer, MEGC was detected in consecutive 29 (1.5%) of 1890 cases. Non-MEGC was in 1860 (98.5%) of 1890 cases and further divided into nonmicropapillary Lauren intestinal-type (58.9%; 1112/1890) and Lauren diffuse-type early gastric carcinoma (39.6%; 749/1890) subgroups.

As shown in Table 1, there was no significant difference in patient mean age, sex, macroscopic growth pattern, tumor size, and perineural invasion frequency among the 3 groups. However, MEGC was significantly more frequently detected in the gastric cardia (31.0%; 9/29) than the nonmicropapillary Lauren diffuse-type early gastric carcinoma (11.2%; 84/749) group ($P < .01$). The percentages of submucosal invasion (93.1% versus 51.8% and 52.1%, $P < .001$), lymphovascular invasion (48.2% versus 9.71% and 14.8%, $P < .001$), and LNM (44.8% versus 9.35% and 24.6%, $P < .05$) were significantly higher in MEGC than in the non-MEGC Lauren intestinal- or diffuse-type groups. The proportion of cases at advanced pathologic stages was also significantly higher in the MEGC group than in the non-MEGC Lauren intestinal-type group (20.7% versus 2.4%; $P < .01$), but not in the non-MEGC Lauren diffuse-type group (10.8%).

3.2. Histopathologic analysis

Microscopically, the micropapillary carcinoma component in early gastric carcinoma was mixed with a component of papillary (n = 17), tubular (n = 9), tubulopapillary (n = 2), or tubular/poorly cohesive carcinoma (n = 1). The neoplastic cells of the micropapillary component in all, except one, exhibited an eosinophilic, pale, finely granular to dense cytoplasm. Only 1 tumor with a component of mixed tubular/

Table 1 Comparison of clinicopathological features between micropapillary and nonmicropapillary Lauren intestinal- or diffuse-type early gastric carcinoma

Feature	MEGC (n = 29)	Nonmicropapillary Lauren intestinal-type early gastric carcinoma (n = 1112)	*P*	Nonmicropapillary Lauren diffuse-type early gastric carcinoma (n = 749)	*P*
Age (y)			.812		.075
≤62	14	512		483	
≥63	15	600		266	
Sex			.615		.174
Male	21	850		448	
Female	8	262		301	
Macroscopic type			.777		.687
0-I/IIa/IIb/IIc	21	831		516	
0-III	8	281		233	
Location			.999		.003
Cardia	9	345		84	
Non-cardia	20	767		665	
Tumor size (cm)			.195		.460
≤2	15	706		439	
>2	14	406		310	
Tumor invasion depth			.000		.000
M3	2	536		359	
SM1/SM2	27	576		390	
Lymphovascular invasion			.000		.000
Present	14	108		111	
Absent	15	1004		638	
Perineural invasion			.148		1.000
Present	2	25		47	
Absent	27	1087		702	
LNM			.000		.014
Present	13	104		184	
Absent	16	1008		565	
Pathologic stage			.000		.175
pI	23	1085		668	
pII/III	6	27		81	

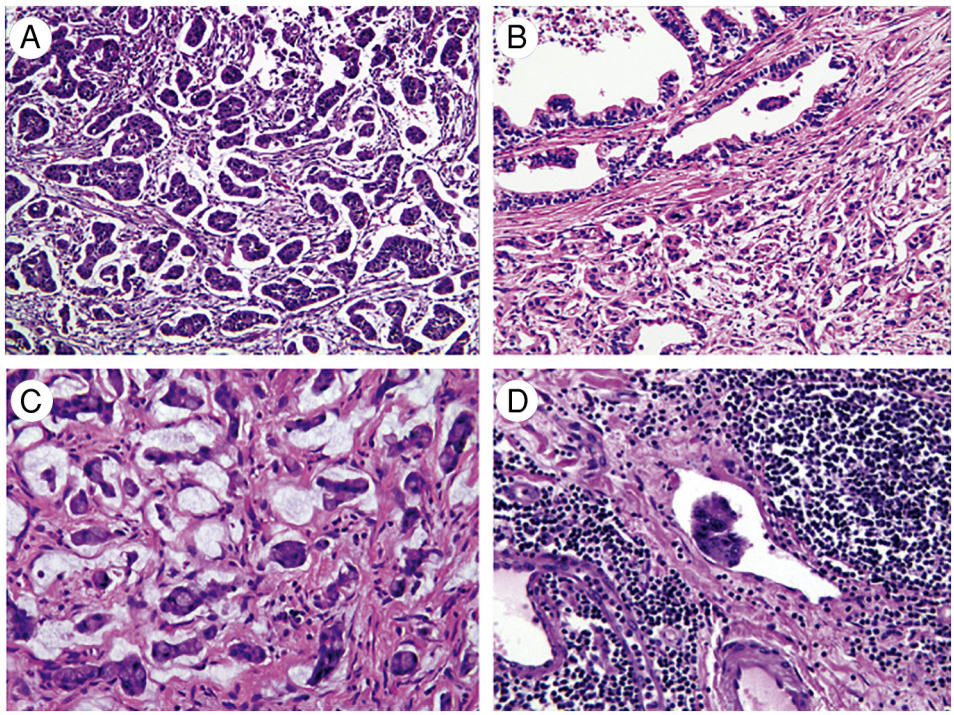

Fig. 2 Histopathologic characteristics of MEGC. A, Micropapillary tumor clusters without fibrovascular cores were surrounded by empty lacunar spaces. B, MEGC (right lower quadrant) was immediately adjacent to a predominant component of papillary adenocarcinoma (left upper quadrant) with a sharp transition. C, MEGC showed signet ring cell morphology in micropapillae. D, The tumor embolus retained the morphology of micropapillary carcinoma. Hematoxylin and eosin, original magnifications ×40 (A and B) and ×200 (C and D).

poorly cohesive carcinoma showed the morphology of signet-ring cells with a central clear globoid droplet of cytoplasmic mucin and eccentrically displaced nuclei. Overall, the nuclear polymorphism and atypia were moderate. Rare mitoses were observed in micropapillary carcinoma (Fig. 2). LNM was identified in 11 MEGC cases on routine hematoxylin-eosin–stained sections and discovered in 2 additional cases with a positive pancytokeratin immunostain in lymph nodes that were initially diagnosed as the absence of carcinoma metastasis on routine hematoxylin-eosin–stained sections (Fig. 3).

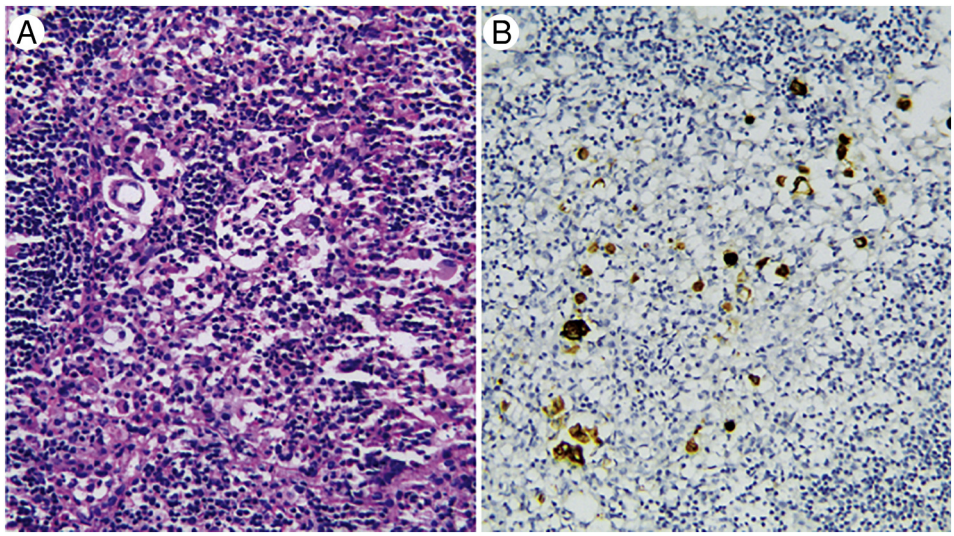

Fig. 3 Pancytokeratin immunostain revealed micrometastasis in a lymph node previously diagnosed as the absence of carcinoma metastasis on a routine hematoxylin-eosin–stained section. A, Inconspicuous tumor clusters and isolated atypical cells in the lymph node. B, Immunohistochemical staining for pancytokeratin of the same tissue block highlights the metastatic carcinoma foci. Hematoxylin and eosin, original magnification ×200 (A); immunohistochemistry, original magnification ×200 (B).

Table 2 Clinicopathological features of MEGC

Case	Sex	Age (y)	Macroscopic type	Tumor location	Size (cm)	Micropapillary component (%)	Histologic type	Invasion depth	Lymphovascular invasion	Perineural invasion	LNM	Pathologic stage	Follow-up (mo)	Status
1	Male	66	0-IIa	Fundus	2	15	Tubular + poorly cohesive	SM1	−	−	+	IB	68	Alive without disease
2	Male	47	0-I	Cardia	2	10	Tubular	SM2	+	−	−	IA	43	Alive without disease
3	Male	53	0-IIa	Antrum	4	15	Tubular	SM2	−	−	+	IB	20	Dead of disease
4	Male	53	0-IIc	Antrum	1.9	30	Tubular	SM2	+	−	+	IB	−	Not available
5	Male	56	0-IIa	Antrum	3	5	Papillary	SM2	+	−	+	IIB	7	Dead of disease
6	Male	58	0-IIc	Antrum	2.3	5	Papillary	SM1	+	−	−	IA	130	Alive without disease
7	Female	58	0-III	Angularis	2	60	Papillary	SM1	−	−	−	IA	145	Alive without disease
8	Female	60	0-IIa	Angularis	5	10	Tubulopapillary	SM2	+	−	+	IIIB	9	Dead of disease
9	Male	61	0-I	Antrum	4	5	Papillary	SM2	+	−	+	IIA	47	Dead of disease
10	Male	64	0-I	Antrum	3	10	Papillary	SM2	+	−	+	IIA	25	Dead of disease
11	Male	69	0-III	Antrum	2.8	5	Papillary	M3	−	−	−	IA	109	Alive without disease
12	Male	78	0-III	Corpus	2	5	Tubular	SM2	−	−	−	IA	32	Alive without disease
13	Male	61	0-III	Corpus	2	25	Tubular	SM2	−	−	−	IA	3	Dead of disease
14	Male	65	0-III	Antrum	3	15	Tubular	SM2	+	−	+	IB	44	Alive without disease
15	Male	70	0-III	Angularis	4	5	Papillary	SM2	+	−	+	IIA	22	Dead of disease
16	Male	60	0-III	Antrum	3	40	Papillary	SM2	+	+	+	IB	−	Not available
17	Male	53	0-IIb	Angularis	3	30	Papillary	SM2	+	−	−	IA	51	Alive with disease
18	Female	58	0-IIb	Antrum	2.5	10	Papillary	SM2	+	−	−	IA	77	Alive without disease
19	Female	63	0-IIc	Antrum	2	5	Papillary	SM2	+	+	+	IIB	54	Dead of disease
20	Male	53	0-IIc	Antrum	3	5	Papillary	M3	−	−	−	IA	−	Not available
21	Male	67	0-IIc	Cardia	2	10	Papillary	SM2	−	−	−	IA	112	Alive without disease
22	Male	71	0-III	Cardia	1.7	10	Tubular	SM2	−	−	−	IA	40	Alive without disease
23	Female	47	0-IIc	Cardia	1.3	5	Papillary	SM2	−	−	−	IA	39	Alive without disease
24	Female	58	0-I	Cardia	1.9	5	Papillary	SM2	−	−	+	IB	35	Alive without disease
25	Male	70	0-I	Cardia	2	20	Tubular	SM2	−	−	−	IA	12	Dead of disease
26	Male	68	0-I	Cardia	1.8	5	Tubulopapillary	SM2	+	−	−	IA	35	Alive without disease
27	Male	70	0-IIa	Cardia	2.2	10	Papillary	SM2	−	−	−	IA	50	Alive with disease
28	Female	59	0-IIa	Cardia	3.3	10	Papillary	SM2	−	−	+	IB	64	Alive without disease
29	Female	62	0-IIa	Angularis	2	5	Tubular	SM2	−	−	−	IA	47	Alive without disease

The morphology of nodal metastatic tumors exhibited either pure micropapillary features or tubulopapillary or mixed tubular/papillary/micropapillary adenocarcinomas. As shown in Table 2, lymphovascular invasion was identified in 14 (48.2%) of 29 cases, in which 9 (64.3%) of 14 demonstrated LNM.

3.3. Risk factors of LNM

Overall, the average number of lymph nodes retrieved was 17.0 per case. Of 301 (15.9%) of 1890 tumors with LNM, 187 (62.1%) were at pathologic stage pIB (pN1), 79 (26.3%) were at pIIA (pN2), 32 (10.6%) were at pIIB (pN3a), and 3 (1.0%) were at pIIIB (pN3b), respectively. The absence of LNM was demonstrated in 1589 (84.1) of 1890 cases.

Risk factors for LNM in 1890 early gastric carcinomas are summarized in Table 3. By univariate analysis, significant risk factors for LNM included patient age of 62 years or less, female sex, excavated gross pattern, noncardiac location, tumor size of greater than 2 cm, submucosal invasion, Lauren diffuse-type, perineural invasion, lymphovascular invasion, and MEGC. Multivariate analysis revealed independent risk factors of LNM as follows: MEGC, patient age of 62 years or less, excavated gross pattern, female sex, noncardiac location, tumor size of greater than 2 cm, submucosal invasion, Lauren diffuse-type, and lymphovascular invasion (Table 3).

In MEGC, predictive risk factors for LNM are summarized in Table 4. By univariate analysis, MEGC mixed with papillary adenocarcinoma or poorly cohesive carcinoma ($P < .05$), and lymphovascular invasion ($P < .05$) were significantly associated with LNM, whereas patient mean age, sex, tumor macroscopic pattern, location, size, invasion depth, perineural invasion, and micropapillary component volume percentage were not. By multivariate analysis, neither the mixed papillary/poorly cohesive carcinoma type nor lymphovascular invasion was an independent risk factor.

3.4. Survival analysis

Of 29 MEGC patients, 3 (10.3%) were lost to follow-up. The median follow-up period was 43.5 months (range, 3-147 months). At the last follow-up interview, 9 (34.6%) of 26

Table 3 Risk factors of LNM in early gastric carcinoma by univariate and multivariate analyses

Feature	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*P*	Odds ratio (95% confidence interval)	*P*
Age (y)		.000		.020
≥63	Reference		Reference	
≤62	1.691 (1.310-2.182)		1.433 (1.059-1.941)	
Sex		.000		.000
Male	Reference		Reference	
Female	1.819 (1.411-2.345)		1.738 (1.289-2.343)	
Macroscopic type		.001		.046
0-I/IIa/IIb/IIc	Reference		Reference	
0-III	1.569 (1.208-2.038)		1.364 (1.005-1.851)	
Tumor location		.000		.001
Cardia	Reference		Reference	
Noncardia	3.232 (2.169-4.818)		2.221 (1.373-3.593)	
Tumor size (cm)		.000		.004
≤2	Reference		Reference	
>2	2.156 (1.680-2.765)		1.521 (1.140-2.028)	
Tumor invasion depth		.000		.000
Intramucosa	Reference		Reference	
Submucosa	4.255 (3.164-5.722)		2.809 (2.008-3.929)	
Lauren classification		.000		.000
Intestinal	Reference		Reference	
Diffuse	2.816 (2.186-3.627)		2.403 (1.773-3.255)	
Perineural invasion		.000		.434
Absent	Reference		Reference	
Present	4.125 (2.554-6.664)		1.257 (0.709-2.227)	
Lymphovascular invasion		.000		.000
Absent	Reference		Reference	
Present	9.506 (7.036-12.843)		6.140 (4.339-8.689)	
Micropapillary carcinoma		.000		.013
Yes	Reference		Reference	
No	4.435 (2.111-9.319)		3.180 (1.275-7.935)	

Table 4 Risk factors of LNM in MEGC by univariate and multivariate analyses

Feature	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*P*	Odds ratio (95% confidence interval)	*P*
Age (y)		.202		
≤62	Reference			
≥63	0.375 (0.083-1.693)			
Sex		.730		
Male	Reference			
Female	1.333 (0.260-6.828)			
Macroscopic type		.407		
0-I/IIa/IIb/IIc	Reference			
0-III	0.500 (0.097-2.577)			
Tumor location		.114		
Cardia	Reference			
Noncardia	4.278 (0.706-25.919)			
Tumor size (cm)		.095		
≤2.0	Reference			
>2.0	3.750 (0.794-17.720)			
Tumor invasion depth		.244		
M3/SM1	Reference			
SM2	4.000 (0.388-41.228)			
Mixed histologic type		.033		.051
Tubular	Reference		Reference	
Papillary/poorly cohesive	7.071 (1.167-42.846)		6.664 (0.990-44.872)	
Perineural invasion		.999		
Absent	Reference			
Present	2.350×10^9 (0.000-)			
Lymphovascular invasion		.048		.081
Absent	Reference		Reference	
Present	4.950 (1.017-24.095)		4.641 (0.827-26.042)	
Micropapillary component		.438		
≤10%	Reference			
>10%	1.875 (0.382-9.197)			

patients died and 2 (7.7%) of 26 were alive but showed distant metastasis. The 3- and 5-year OS rates of patients with MEGC were 73.1% and 58.6%, respectively.

4. Discussion

In this multicenter study with 29 MEGC radical resection cases, we demonstrated a bleak clinicopathological profile for this extremely rare (1.5%) early gastric carcinoma with the following characteristics: (1) as an independent risk factor for LNM, (2) a high propensity for lymphovascular invasion (48.2%; 14/29) and LNM (44.8%; 13/29), (3) remarkable frequency (93.1%; 27/29) for submucosal invasion, (4) high prevalence in cases diagnosed at advanced stages (20.7%; 6/29), and (5) low 5-year OS rate (58.6%). The constellation of pathologic evidence illustrated in this multicenter study suggests an aggressive pathobiologic behavior of MEGC and lends support to a surgical but not endoscopic therapy strategy for this unusual type of early gastric carcinoma.

As reported in carcinoma of other organs [9,20,21], micropapillary carcinomas of the stomach are also aggressive. Our findings on MEGC confirmed and extended the results of previous single-center study reports [14-16,22]. Among aforementioned several worrisome pathologic characteristics of MEGC, the alarmingly high frequency of 44.8% of MEGC cases with LNM is particularly devastating. Even in cases without LNM diagnosed on hematoxylin-eosin–stained sections, LNM may be uncovered with a positive pancytokeratin immunostain, as reported in lung micropapillary adenocarcinoma [9]. The high risk for MEGC for lymphovascular invasion and LNM may be related to abnormal cell-cell adhesion and activation of transcription factors for cell proliferation [15]. We would recommend performing a routine pancytokeratin immunostain on negative lymph nodes in all MEGC cases after routine histopathologic evaluation of hematoxylin-eosin–stained sections. This would help minimize the chances for understaging of this rare variant of early gastric carcinoma with dismal prognosis.

Micropapillary carcinoma is a recently descripted variant of carcinoma [8,10,12,15,23]. Because the proportion of the micropapillary component required for the diagnosis of this rare carcinoma has not yet been established, most investigators use the 5% cutoff for the micropapillary component

[13,15,24], as we adopted in this study. As reported previously, the prevalence of this rare gastric carcinoma may be higher in advanced gastric carcinoma [13,14] than in early gastric carcinoma [8,15,25]. Therefore, when dealing with small gastric cancer biopsy specimens, surgical pathologists may need to thoroughly investigate biopsy tissues for a small micropapillary component in every case.

Microscopically, MEGC may show the same distinctive histologic pattern as micropapillary carcinoma in other organs, which is characterized by small papillary clusters within empty lacunar spaces without a true fibrovascular core. The stroma-facing neoplastic cells may show apical secretory properties [13,24,26], as illustrated in our study. In general, the micropapillary component in early gastric carcinoma is usually minute and mixed with a predominant papillary and/or tubular adenocarcinoma component in most cases and occasionally with mucinous, or poorly differentiated adenocarcinoma in some cases [13,15,16,22,23,25,26]. The characteristic inside-out pattern of micropapillary carcinoma can be confirmed immunohistochemically for epithelial membrane antigen or MUC1 with peculiar linear immunoreactivity on the outside of neoplastic cell clusters [10,16,27,28]. Although other molecular markers, such as CD10 and KL-6, have been reported to diagnose micropapillary carcinoma [25,29,30], none are specific, and the diagnosis of micropapillary carcinoma is primarily based on the morphologic characteristics of this unique carcinoma variant on a routine hematoxylin-eosin stain.

The most important differential diagnosis of MEGC is tumor emboli, which may be ruled out by D2-40 and CD34 immunostains in challenging cases. Occasionally, tissue processing artifact may result in pseudomicropapillary morphology, mimicking MEGC. However, tumor cell clusters with retraction artifact retain the morphology of conventional adenocarcinoma and lack the apical secretory properties in the stroma-facing surface of MEGC. In problematic cases, an epithelial membrane antigen or MUC1 immunostain may help demonstrate the reversed polarity of MEGC [14,25,26]. Metastatic micropapillary carcinoma from the ovary, urinary tract, and other organs to the stomach should also be excluded [31,32]. Overall, the distinct morphologic features of MEGC should not have major diagnostic challenges in most cases.

Because of a propensity of MEGC for lymphovascular invasion and LNM, and dismal prognosis, as shown in this and previous single-center studies [6,14], clinical management of patients with MEGC should differ from that with conventional early gastric carcinoma of other histologic subtypes. In addition to other risk factors of LNM, such as lymphovascular invasion and submucosal invasion, reported in our earlier multicenter study [33], the multivariate analysis in the present study identified MEGC as another independent risk factor for LNM. Our data provide the persuasive evidence against the conservative endoscopic therapy for this rare but aggressive early gastric carcinoma variant.

The major limitations of this multicenter study are several. First, the retrospective study design inherits potential selection bias, which was, however, minimized by collecting consecutive cases for this project. We followed a strict quality control protocol, in which all study pathologists were trained with the WHO diagnostic criteria on early gastric carcinoma; the diagnosis of every MEGC case was confirmed by at least 2 pathologists and also verified by the senior pathologist (Q. H.), who frequently conducted random audits at each participating center to ensure early gastric carcinoma diagnostic accuracy and consistency. Second, we did not complete the follow-up interview in all 29 patients, and 3 (10%) patients were lost to follow-up. Given that the 5-year OS rate of 26 MEGC patients was worse than that (80.5%-96.8%) in a previous single-center study [34] and 2 additional patients demonstrated distant metastasis but were alive at the last interview, MEGC patient survival might be even poorer. Importantly, the current data set has the largest number of 1890 eligible early gastric carcinomas with 29 MEGC cases, which is unprecedented for studies of MEGC. We are confident that the data reported in this multicenter study are reasonably sound.

In summary, the results of this multicenter study on 29 MEGC radical gastrectomies showed aggressive clinicopathological features with high risk for LNM, lymphovascular invasion, advanced pathologic stages, and grim prognosis. The strong clinicopathological evidence presented in this study argues for a proactive surgical, rather than endoscopic, treatment strategy for patients with MEGC.

Acknowledgments

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