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Original Article

Risk Factors of Microscopic Invasion in Early Gastric Cancer

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ABSTRACT

Purpose: This study aimed to evaluate the clinical significance of microscopic invasion to determine the adequate resection margin in early gastric cancer (EGC).
Materials and Methods: A retrospective review was performed that included patients who underwent gastrectomy for clinical early gastric cancer (cEGC) at Seoul National University Hospital between January 2007 and December 2010. After subtracting the microscopic resection margin from the gross resection margin for each proximal or distal resection margin, microscopic invasion was represented by the larger value. Microscopic invasion and its risk factors were analyzed according to the clinicopathologic characteristics.
Results: In total, 861 patients were enrolled in the study. Microscopic invasion of cEGC was 6.0±12.8 mm, and the proportion of patients with microscopic invasion ≥0 mm was 78.4%. In the risk group, tumor location, pT stage, and differentiation did not significantly discriminate the presence of microscopic invasion. The microscopic invasion of EGC-IIb was 13.9±16.8 mm, which was significantly greater than that of EGC-I. No linear correlation was observed between the overall tumor size and microscopic invasion (R=0.030). The independent risk factors for microscopic invasion ≥20 mm were EGC-IIb vs. EGC-I/IIa/IIc/III (odds ratio [OR], 3.103; 95% confidence interval [CI], 1.533–6.282; P=0.002) and male vs. female sex (OR, 1.655; 95% CI, 1.012–2.705; P=0.045).
Conclusions: Male sex and EGC-IIb were independent risk factors for microscopic invasion ≥20 mm. Examination of intraoperative frozen sections is highly recommended to avoid resection margin involvement, especially in cases of EGC-IIb.

Keywords: Stomach neoplasm; Risk factors

INTRODUCTION

As nationwide health screening has increased the detection of early gastric cancer (EGC) in Korea, the number of cases of EGC has gradually increased [1,2]. Minimally invasive surgery has become the mainstay of treatment for EGC, and an adequate resection margin is one of the most important prognostic factors for the local recurrence of EGC [3]. In addition to the oncologic importance of the resection margin, the preservation of a larger remnant stomach in function-preserving surgery is significantly related to the appropriate resection margin, especially in EGC. Therefore, the importance of accurate localization and

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Author Contributions

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Conflict of Interest

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

evaluation of peritumoral invasion is gradually increasing. However, in the era of minimally invasive surgery, direct localization has become increasingly difficult because tactile access to the tumor or the gastric wall itself is extremely limited. In addition, preoperative endoscopic clipping, a widely used localization technique, depends on gross tumor findings, and thus, this method has similar limitations in the evaluation of peritumoral microscopic invasion.

The Japanese Gastric Cancer Treatment Guidelines recommend a resection margin of 2 cm for T1 tumors and 3 cm for T2 tumors regardless of primary tumor size, differentiation, or gross type [4]. The National Comprehensive Cancer Network guidelines recommend a resection margin greater than 4 cm from gross tumors with T1b–T3 invasion [5]. These guidelines recommend a specific length of the resection margins, but insufficient scientific evidence supports the size of these margins, especially in EGC. Though a few studies have suggested an appropriate resection margin for EGC, the standard length of a safe margin has not been established [6-8]. An inconsistent resection margin could primarily result from a wide range of microscopic tumor invasion depths, but it is difficult to estimate microscopic invasion before or during surgery, especially during minimally invasive surgery. In advanced gastric cancer (AGC), a resection margin larger than we can predict is usually required because of the high rate of locoregional recurrence, frequent submucosal spread of cancer cells, and adjacent plication deformity [9]. However, comprehensive analysis of microscopic tumor invasion according to various clinicopathologic factors in EGC could be more useful because of lower locoregional recurrence rates after precise margin-free resection and the higher possibility of preservation of function with a larger remnant stomach. Therefore, the purpose of this study was to analyze microscopic invasion as it relates to resection margins according to clinicopathologic parameters in clinical early gastric cancer (cEGC).

MATERIALS AND METHODS

Analysis of perioperative clinicopathologic factors

A retrospective review was performed that included patients who underwent gastrectomy for cEGC, according to the Japanese Gastric Cancer Treatment Guidelines, at Seoul National University Hospital between January 2007 and December 2010. Patients with multiple gross tumor types, multiple tumor locations, tumor spread throughout the stomach, or preoperative gastric cancer-related treatment, including endoscopic resection, were excluded from the data analysis. cEGC was defined when a primary tumor was diagnosed as a T1 lesion by esophagogastroduodenoscopy, endoscopic ultrasound, and computed tomography. The pathologic diagnosis was made according to the 7th edition of the American Joint Committee on Cancer's classification of malignant tumors [10]. Clinicopathologic information included age, sex, operation type, tumor location, gross tumor type, pathologic stage, differentiation, Lauren's classification, tumor size, and resection margin. Gross type was classified according to the Japanese classification of gastric carcinoma (3rd edition) [11]. Regarding differentiation, papillary, well differentiated, and moderately differentiated types were classified as the differentiated group, whereas poorly differentiated, mucinous, and poorly cohesive cell types were classified as the undifferentiated group based on the World Health Organization classification of tumors of the digestive system [12] and the Japanese classification of gastric carcinoma. Tumor size was measured after formalin fixation and subsequent microscopic mapping. Survival data were collected from the records of the Ministry of the Interior of Korea.

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Tumor localization and measurement of the resection margin

The tumor was localized intraoperatively using palpable peritumoral clips, which were placed at the proximal and distal ends 1 cm from the tumor using preoperative endoscopy. The resection margins were determined based on the location of the peritumoral clips. Both the proximal and distal resection margins were routinely verified by examination of intraoperative frozen sections and were finally confirmed by postoperative pathology. For cases in which a positive margin was suspected based on intraoperative frozen section examination, we performed additional resection of the margins or conversion to total gastrectomy. After the final gastrectomy, the resection margins were measured grossly and microscopically. The gross resection margin was measured after the fresh specimen was delivered to the Department of Pathology. After gross evaluation, each resected specimen was spread out and attached to a polystyrene board to avoid rolling of the edges and then fixed in 10% formalin. The gross specimen was placed on a piece of gridded mapping paper and scanned to indicate the specimen boundaries. Specimens were serially sectioned at 4-mm intervals. Each 4-mm section was placed on a slide, stained with hematoxylin-eosin, and examined for the presence of tumor involvement. Based on the results, the borders of the tumor were indicated on the mapping paper, and the length (mm) of the proximal and distal microscopic resection margins was determined. After subtracting the microscopic resection margin from the gross resection margin for each proximal or distal resection margin, the final microscopic invasion was determined to be the larger value between the proximal and distal microscopic invasion. We classified the overall population into 3 groups: the safe group (microscopic invasion of <0 mm), the risk group (microscopic invasion of ≥0 mm), and the high-risk group (microscopic invasion of ≥20 mm) because the Japanese Gastric Cancer Treatment Guidelines recommend a gross resection margin of 2 cm for T1 tumors.

Statistical data analysis and ethics

Student's t-test, the χ^2 test, and 1-way analysis of variance (ANOVA) were used for comparative statistical analyses. Multivariate analysis was performed by binary logistic regression. Recurrence and survival analyses were conducted using the Kaplan-Meier method and the log-rank test. All statistical analyses were performed at a significance level of 5% using SPSS, version 22 (SPSS Inc., Chicago, IL, USA).

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1708-099-879). The requirement for informed consent from the patients was waived. This study was conducted according to the principles of the Declaration of Helsinki.

RESULTS

Risk group vs. safe group

After a retrospective review of 1,192 patients with cEGC, 861 patients were selected for the study pool; 331 patients were excluded based on the criteria described in the methods section. In the analysis of all patients, the male to female ratio was 1.6:1 (526:335), and the mean age of the patients was 58.2±11.5 years. In total, 76.3% of the patients underwent distal gastrectomy, and 10.6% underwent pylorus-preserving gastrectomy. cEGC included 2.8% of pT2 cases and 0.5% of pT3 cases. The average tumor size was 24.7±15.3 mm, and the average microscopic invasion was 6.0±12.8 mm. The microscopic invasion in the risk group was 8.9±12.9 mm, which was significantly greater than that in the safe group (−4.7±3.9 mm)

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Table 1. Comparison between the risk group and the safe group

Variables		Microscopic invasion* ≥0 (n=675)	Microscopic invasion <0 (n=186)	P-value
Age		58.1±11.6	58.6±11.3	0.658
Sex (male:female)		402:273 (1.5:1)	124:62 (2:1)	0.078
Operation type	Distal gastrectomy	512 (75.9)	145 (78.0)	0.295
	Pylorus-preserving gastrectomy	73 (10.8)	18 (9.7)	
	Proximal gastrectomy	47 (7.0)	7 (3.8)	
	Total gastrectomy	43 (6.4)	16 (8.6)	
Tumor location	Lower	416 (61.6)	122 (65.6)	0.369
	Middle	190 (28.1)	51 (27.4)	
	Upper	69 (10.2)	13 (7.0)	
Gross type	EGC-I	10 (1.5)	2 (1.1)	0.328
	EGC-IIa	41 (6.1)	6 (3.2)	
	EGC-IIb	40 (5.9)	13 (7.0)	
	EGC-IIc	578 (85.6)	161 (86.6)	
	EGC-III	6 (0.9)	4 (2.2)	
pT stage	pT1	651 (96.4)	182 (97.8)	0.478
	pT2	20 (3.0)	4 (2.2)	
	pT3	4 (0.6)	0 (0.0)	
Differentiation	Differentiated	363 (53.8)	107 (57.5)	0.363
	Undifferentiated	312 (46.2)	79 (42.5)	
Lauren's classification	Intestinal	371 (55.0)	119 (64.0)	0.089
	Diffuse	260 (38.5)	57 (30.6)	
	Mixed	44 (6.5)	10 (5.4)	
Tumor size (mm)		25.9±15.6	20.3±13.1	<0.001
Gross PRM (mm)		42.7±24.8	43.3±24.8	0.797
Gross DRM (mm)		48.9±29.2	42.5±28.2	0.008
Microscopic PRM (mm)		41.4±26.1	52.3±25.7	<0.001
Microscopic DRM (mm)		46.2±28.4	49.5±46.2	0.161
Microscopic invasion (mm)		8.9±12.9	−4.7±3.9†	<0.001

Values are presented as mean±standard deviation or number (%).
EGC = early gastric cancer; PRM = proximal resection margin; DRM = distal resection margin.
*Microscopic invasion is the subtraction of the microscopic resection margin from the gross resection margin; the larger value between the proximal and distal microscopic invasion was used for as the final microscopic invasion value; †A negative value means that the microscopic tumor area is smaller than the area measured by gross examination.

(**Table 1**). Tumor size in the risk group was significantly larger at 25.9±15.6 mm compared with 20.3±13.1 mm in the safe group. In terms of the gross measurements, the distal resection margin was significantly longer in the risk group than in the safe group (48.9±29.2 vs. 42.5±28.2 mm). In terms of the microscopic measurements, the proximal resection margin was significantly longer in the safe group than in the risk group (52.3±25.7 vs. 41.4±26.1 mm). No significant differences were observed in tumor location, differentiation, Lauren's classification, or other clinicopathologic characteristics between the risk and safe groups. There was no case in which the resection margin was positive according to the final pathologic report when the intraoperative frozen section was negative.

Microscopic invasion in the risk group (n=675)

No significant difference was observed in the length of microscopic invasion based on tumor location or differentiation (**Fig. 1A and B**). According to the pathologic T stage, microscopic invasion was 8.9±13.0 mm for T1 (n=651), 8.2±10.4 mm for T2 (n=20), and 13.5±11.7 mm for T3 (n=4); none of these differences were significant (**Fig. 1C**). In terms of Lauren's classification, the intestinal type had significantly greater microscopic invasion than the diffuse type: 9.9±14.8 vs. 7.7±10.3 mm; P=0.030 (**Fig. 1D**). Regarding the gross type, the microscopic invasion in EGC-IIa was significantly longer than in EGC-I (8.4±9.1 vs. 3.8±2.8 mm; P=0.009), and the microscopic invasion in EGC-IIb was significantly longer than that in EGC-I (13.9±16.8 vs. 3.8±2.8 mm; P=0.001) (**Fig. 2**). No linear correlation was found between

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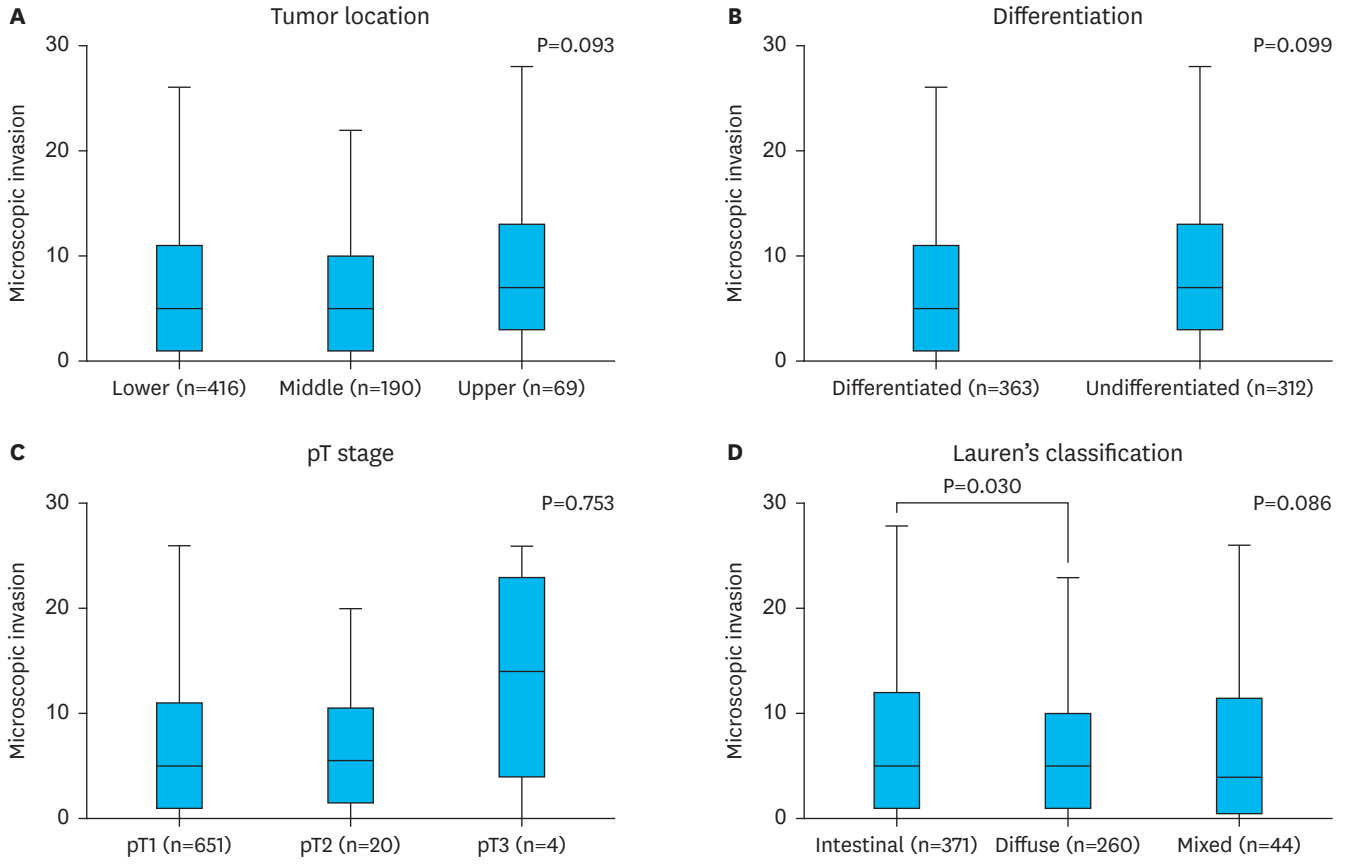

Fig. 1. Distribution of microscopic invasion according to the clinicopathologic characteristics in the risk group. Microscopic invasion according to (A) tumor location, (B) pT stage, (C) differentiation, and (D) Lauren's classification. Boxes indicate the interquartile ranges and median values; whiskers indicate the minimum and maximum values. P-values in the upper right corner were determined by Student's t-test or 1-way ANOVA. P-values in the upper section of the box (D) were generated using Student's t-test.
ANOVA = analysis of variance.

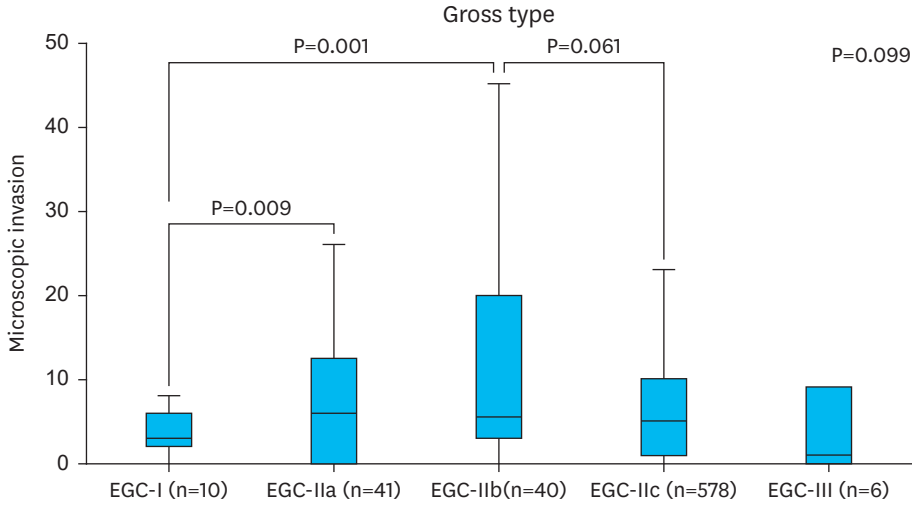

Fig. 2. Distribution of microscopic invasion according to gross type in the risk group. Boxes indicate the interquartile ranges and median values; whiskers indicate the minimum and maximum values. The P-value in the upper right corner was determined by 1-way ANOVA. P-values in the upper section of the box were generated using Student's t-test.
ANOVA = analysis of variance; EGC = early gastric cancer.

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overall tumor size and microscopic invasion (R=0.030) (**Fig. 3A**). In the subgroup analysis of the gross type, EGC-IIa (R=0.46) and EGC-III (R=0.86) demonstrated a linear correlation

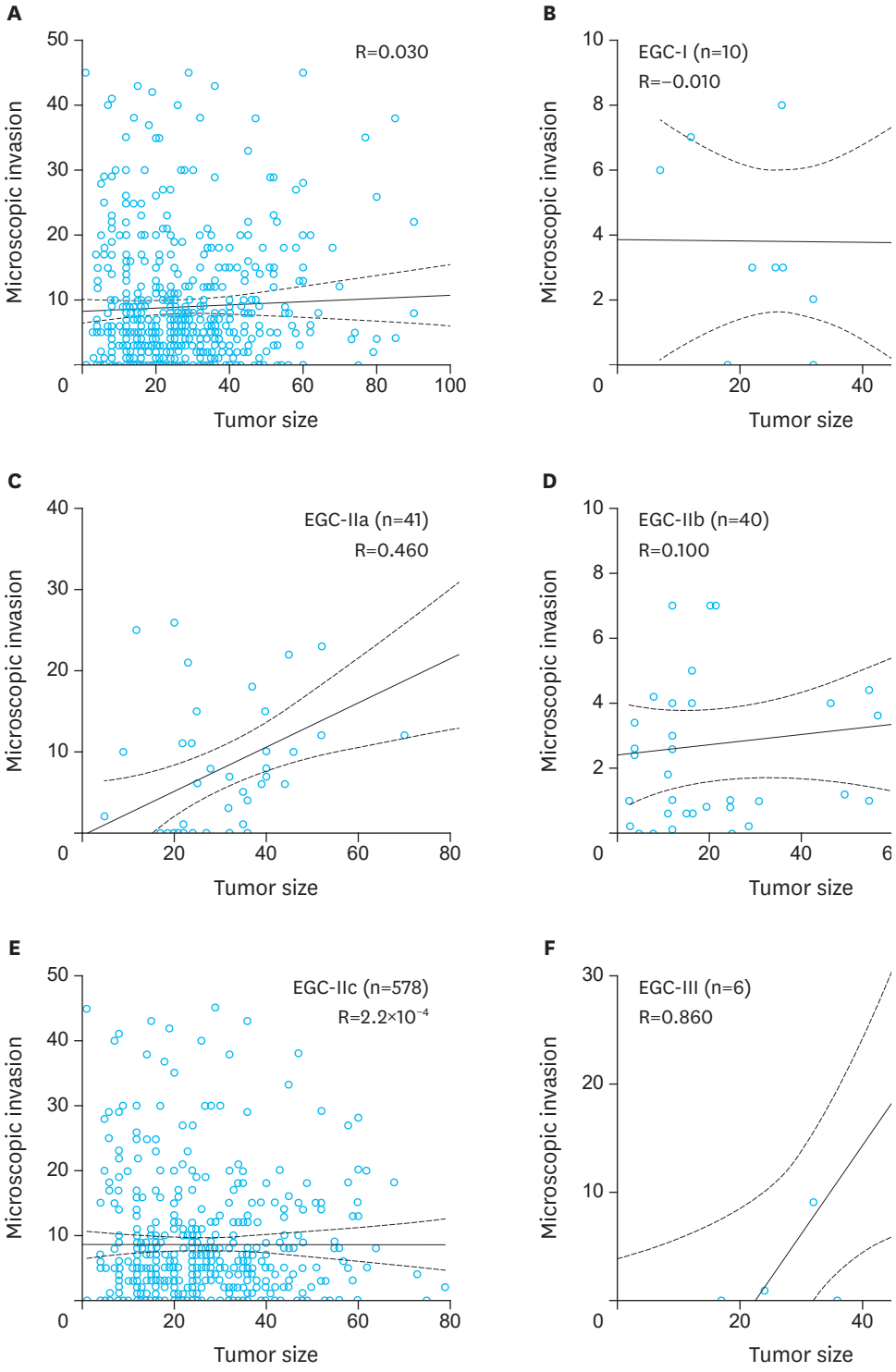

Fig. 3. Distribution of microscopic invasion according to tumor size in the risk group. (A) Entire risk group, (B) EGC-I, (C) EGC-IIa, (D) EGC-IIb, (E) EGC-IIc, and (F) EGC-III. Regression lines, CIs, and correlation coefficients (R) are displayed in the scatter plots.
EGC = early gastric cancer; CI = confidence interval.

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with tumor size. In contrast, no linear correlation with tumor size was observed in EGC-I, EGC-IIb, and EGC-IIc tumors (**Fig. 3B-F**).

Microscopic invasion in the high-risk group

In univariate analysis, the high-risk group contained a significantly higher proportion of male patients, EGC-IIb cases, and advanced T stage disease (**Table 2**). However, multivariate analysis revealed that sex and gross type were independent risk factors that predicted inclusion in the high-risk group.

A significantly higher proportion of male patients were in the high-risk group (71.3%) (odds ratio [OR], 1.655; 95% confidence interval [CI], 1.012–2.705; P=0.045). Moreover, the high-risk group contained a significantly higher proportion of EGC-IIb tumors (13.8%) as opposed to EGC-I/IIa/IIc/III tumors (OR, 2.961; 95% CI, 1.485–5.906; P=0.002).

Survival and recurrence

No significant difference was observed in the overall survival among patients in the safe group, patients with microscopic invasion of 0–20 mm, and patients in the high-risk group (P=0.692) (**Fig. 4A**). This study contained 13 cases of recurrence (1.5%, 13/861); 2 in the safe group (1.1%, 2/186) and 10 in the group with a microscopic invasion of 0–20 mm (1.97%; 10/588) (**Table 3**). In the high-risk group specifically, the recurrence rate was 1.1% (1/87). No significant difference was observed in the recurrence-free survival rate among patients in the safe group, patients with a microscopic invasion of 0–20 mm, and patients in the high-risk group (P=0.796) (**Fig. 4B**).

DISCUSSION

This study presents a scientific basis for the surgical treatment of cEGC via an analysis of the independent risk factors for microscopic invasion. The concept of common resection margins irrespective of various clinicopathologic factors tends to overlook microscopic invasion [13].

Table 2. Microscopic invasion in the high-risk group

Variables		Microscopic invasion ≥2 cm (n=87)	Microscopic invasion <2 cm (n=774)	Univariate analysis P-value	Multivariate analysis	
					OR (95% CI)	P-value
Age		59.4±11.5	58.1±11.5	0.323		
Sex	Female	25 (7.5)	310 (92.5)	0.040		0.045
	Male	62 (11.8)	464 (88.2)		1.655 (1.012–2.705)	
Tumor location	Lower	59 (11.0)	479 (89.0)	0.142		
	Middle	17 (7.1)	224 (92.9)			
	Upper	11 (13.4)	71 (86.6)			
Gross type	EGC-I/IIa/IIc/III	75 (9.3)	733 (90.7)	0.002		0.002
	EGC-IIb	12 (22.6)	41 (77.4)		2.961 (1.485–5.906)	
pT stage	pT1	83 (10.0)	750 (90.0)	0.029		0.084
	pT2	2 (8.3)	22 (91.7)		0.944 (0.216–4.126)	
	pT3	2 (50.0)	2 (50.0)		9.538 (1.308–69.54)	
Differentiation	Differentiated	55 (11.7)	415 (88.3)	0.088		
	Undifferentiated	32 (8.2)	359 (91.8)			
Lauren's classification	Intestinal	58 (11.8)	432 (88.2)	0.105		
	Diffuse	23 (7.3)	294 (92.7)			
	Mixed	6 (11.1)	48 (88.9)			
Tumor size (mm)		27±22	24±14	0.085		

Values are presented as mean±standard deviation or number (%).
OR = odds ratio; CI = confidence interval; EGC = early gastric cancer.

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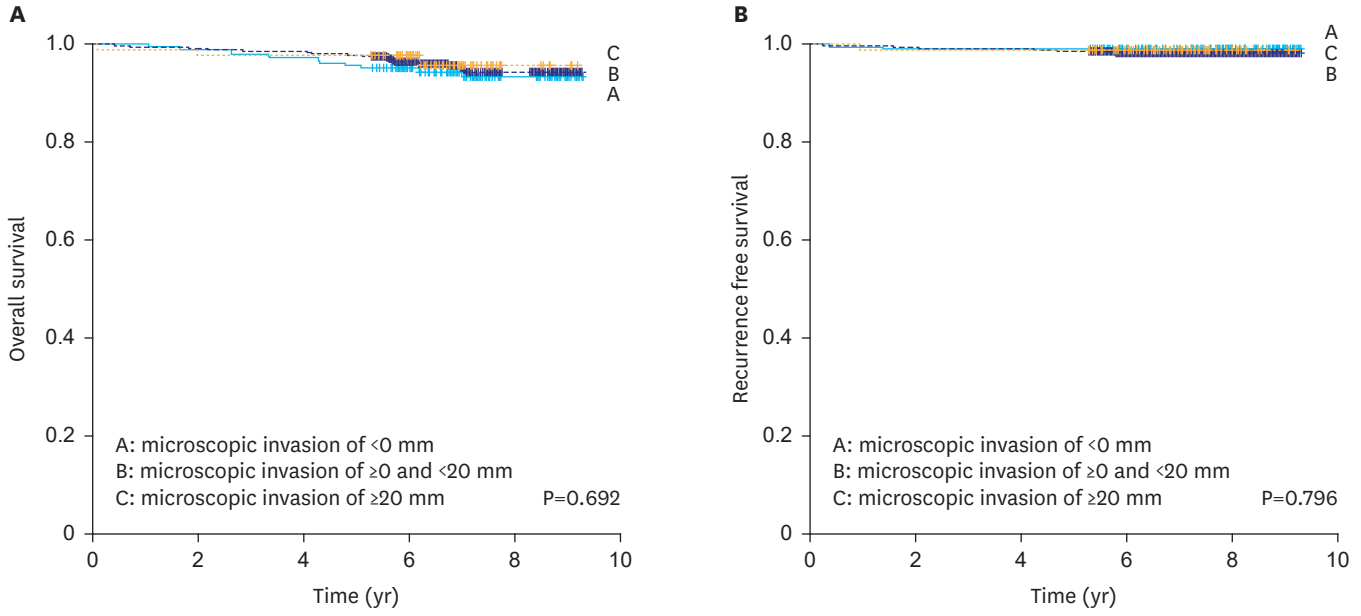

Fig. 4. Survival analysis according to microscopic invasion. (A) Overall survival (P=0.692). (B) Recurrence-free survival (P=0.796). Each line is presented safe group (microscopic invasion of <0 mm, n=186), microscopic invasion of ≥0 and <20 mm (n=588), and high-risk group (microscopic invasion of ≥20 mm, n=87).

Table 3. Recurrence pattern in detail

Variables	Total (n=861)	Safe group (n=186)	Microscopic invasion 0–20 mm (n=588)	High-risk group (n=87)	P-value
No. of any recurrence	13 (1.5)	2 (1.1)	10 (1.7)	1 (1.1)	0.843
Locoregional					
Anastomosis	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0.793
Remnant stomach	4 (0.5)	0 (0.0)	4 (0.7)	0 (0.0)	0.393
Distant					
Distant lymph node	3 (0.3)	1 (0.5)	1 (0.2)	1 (1.1)	0.311
Hematogenous (liver, bone)	3 (0.3)	1 (0.5)	2 (0.3)	0 (0.0)	0.780
Peritoneal	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0.628

Values are presented as number (%). The P-value was calculated between the safe group (microscopic invasion of <0 mm), microscopic invasion of ≥0 and <20 mm, and high-risk group (microscopic invasion of ≥20 mm).

The previous treatment for cEGC has been largely replaced by minimally invasive surgery. As most cEGC tumors cannot be palpated, preoperative endoscopic clipping is used to ascertain the tumor location prior to surgery. The resection margins could be planned by the manual palpation of this clip [14]. During intracorporeal anastomosis, intraoperative endoscopy is considered an alternative method because clips cannot be palpated before resection with this method [15]. However, as preoperative clipping or intraoperative endoscopy is performed based on gross tumor findings, these techniques offer simple information assuming a gross tumor border; moreover, the evaluation of microscopic invasion before surgery is not possible [16]. Therefore, surgeons predict the appropriate resection margins based on their own experience or consideration of various clinicopathologic factors, including differentiation, size, and gross tumor type. However, the relationship between these clinicopathologic factors and microscopic invasion has not been scientifically evaluated. Our study offers comprehensive information for the determination of a more appropriate resection margin in cEGC according to various clinicopathologic parameters.

Our study evaluated the efficacy of the current guidelines in the high-risk group. When the resection margin, as recommended by the guidelines, was applied to EGC-IIb, we found a 22.6% probability of a tumor-positive resection margin in cEGC. The resection margin

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can be determined with no significant difference up to pT2 in cEGC. Although our study did not show a significant difference in microscopic invasion according to pT stage, the microscopic invasion of pT3 tumors (13.5±11.7 mm) tended to be longer than that of T1 and T2 tumors. However, the sample size of pT3 cases (n=4) was too small to ensure statistical power. Therefore, if the tumor is suspected to have T3 invasion, we recommend that careful attention is paid to ensure a sufficient resection margin, even in cEGC.

For EGC-IIb cases, the superficial flat type, it is usually difficult to identify the exact tumor border upon gross inspection. The tumor border can be confused with simple mucosal erosion or chronic inflammation because it sometimes appears as a slightly erythematous flat lesion. In this study, the proportion of EGC-IIb cases was 6.2% (53/861); this percentage was 0.4% according to the Paris endoscopic classification [16] and was reported as 8.7% in another study [17]. Tools to enhance visualization, such as narrow band imaging magnification endoscopy, which are not always effective at determining microscopic invasion, have been developed [18]. In addition, the submucosal spread of diffuse or undifferentiated tumors is considered a worse prognostic factor, especially in type IV AGC, and a larger resection margin is recommended compared to that of other tumor types [9]. However, we observed that the microscopic invasion of diffuse and undifferentiated cases was not significantly different in cEGC. There have been few biological studies on the oncologic behavior of microscopic invasion or the submucosal spread of EGC. Recently, based on the "soil to seed" hypothesis, studies have reported that proteins expressed in cancer margins are different from those expressed in normal tissues [19]. An analysis of protein or RNA expression at microscopic invasion sites of EGC-IIb and other tumors will provide useful information about specific biological factors that explain this different phenotype and the extensive spread of gastric cancer.

The guarantee of a safe resection margin affects recurrence and the survival of gastric cancer patients [20]. A longer microscopic invasion is likely to correspond with a shorter resection margin, which was observed in our study. However, the results of our study revealed no difference in recurrence-free survival among patients in each group based on microscopic invasion length. Our previous study revealed that even if tumor cells are found in the resection margin, no difference exists in the survival rate if a safe margin is obtained through re-resection, especially in EGC [21]. At our institution, intraoperative frozen section analysis is performed as a routine process and is one of the most important procedures for obtaining a clear resection margin during surgery, which results in a similar prognosis among different microscopic invasion groups [22]. In this study, no case was observed in which the resection margin was positive in the final pathologic report when the intraoperative frozen section was negative. The current guidelines suggest only simple information regarding the resection margin according to whether the patient has EGC or AGC. Our comprehensive analysis of microscopic invasion could provide useful scientific evidence to update these guidelines and will also be helpful to decrease the re-resection rate, to decrease the intraoperative conversion to total gastrectomy, and to obtain a greater volume of the remnant stomach after precise resection for EGC even in such institutions where routine frozen section analysis is not available.

The limitations of the study are the sample size and the application range. First, we included insufficient sample sizes of the gross types of EGC-I and EGC-III. In fact, EGC-I and EGC-III represented 1.4% and 1.2%, respectively, of the cases in our study. In the 2014 National Survey of the Korean Gastric Cancer Society, EGC-I and EGC-III formed a small percentage

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of the total number of gastric cancer cases: 4.6% and 5.3%, respectively [23]. Therefore, this small proportion of EGC-I and EGC-III may not be an institution-specific selection bias, but nevertheless, a multi-center study is required for a more accurate analysis of these rare cases. Second, we excluded tumors of the mixed gross type (n=146) from the study and thus cannot provide information on this type. For the mixed gross type, inter-observer variation can have a large effect on the results of a study. When accurate guidelines for mixed gross typing are developed or when the biological characteristics of a single gross type are known, additional studies can be performed in future.

To the best of our knowledge, this is the first study to statistically evaluate microscopic invasion and its relationship to resection margins in EGC. In conclusion, the gross tumor type showed a significantly different microscopic invasion in cEGC. In particular, EGC-IIb was the only independent risk factor for microscopic invasion ≥20 mm. Surgeons should pay greater attention to obtaining sufficient margins when they perform gastrectomy in patients with EGC-IIb. Intraoperative frozen section analysis is also highly recommended to avoid resection margin involvement, especially in EGC-IIb cases.

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