

Predictive Factors and Long-Term Outcomes of Early Gastric Carcinomas in Patients with Non-Curative Resection by Endoscopic Submucosal Dissection

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Purpose: Non-curative resection (NCR) remains problematic in some cases of early gastric carcinomas (EGCs) treated by endoscopic submucosal dissection (ESD). The aim of this study was to identify predictors of NCR, especially of eCura C1 and eCura C2 resections, before ESD and study long-term outcomes of EGC patients with NCR.

Patients and Methods: A retrospective review of medical records was conducted over an 8-year period for EGCs undergoing ESD. Clinicopathologic and endoscopic characteristics and patients' survival were analyzed. Risk factors for NCR and eCura C1 and C2 resections were assessed by logistic analyses. Survival of patients was estimated with the Kaplan–Meier method with a Log rank test.

Results: A total of 463 patients with 472 lesions were qualified. By univariate and multivariate analyses, the predictors for NCR and eCura C2 resections were tumor size >20 mm, tumors located in cardia-fundus, uneven surface, margin elevation, and mixed and undifferentiated types, and those for eCura C1 resection were tumors located in cardia-fundus, negative lifting sign, and mixed and undifferentiated types. The 5-year cancer-specific and cancer-free survival rates were 100.0% and 94.2%, and 95.3% and 83.4% in the curative resection (CR) and NCR groups, respectively. The 5-year cancer-specific and cancer-free survival rates were significantly greater in the CR group than that in the NCR group ($P < 0.0001$).

Conclusion: In this cohort, we identified various endoscopic and pathologic features of EGCs to predict NCR, especially eCura C1 and eCura C2 resections before ESD. These clinically valuable factors would be very informative to endoscopists and surgeons who perform ESD to resect EGCs.

Keywords: early gastric carcinoma, endoscopic submucosal dissection, non-curative resection, long-term outcome, stomach

Introduction

Gastric carcinoma is the fifth most common cancer and the third leading cause of cancer-related deaths in the world.¹ At present, the only hope for better survival of gastric cancer patients is early detection and prompt resection of early gastric carcinoma (EGC), which is defined as invasive carcinoma restricted to the mucosa and submucosa of the stomach, regardless of the presence or absence of lymph node metastasis (LNM).² With the advancement of endoscopic techniques and instruments,

early detection of EGCs has been improved dramatically over the past decade.³ For EGC cases with a negligible risk of LNM, endoscopic submucosal dissection (ESD) has been recognized as a beneficial procedure for resection because of high therapeutic efficacy, low prevalence of complications, and excellent quality of postoperative life, compared to surgical resection.^{4–9}

In reality, despite a strict application of those “absolute” and “expanded” rules for ESD resection of EGC tumors in the pre-operative assessment, many cases with residual tumors or the risk of LNM are discovered by histopathologic examination after ESD resection. For those outliers, the ESD resection is considered as non-curative resection (NCR). Previous studies have shown NCR rates ranging from 11.9% to 21.4% of ESD-resected EGC cases.^{10–15} After non-curative ESD resection, the incidence of residual carcinomas and the rate of LNM range 24.6–34.9% and 5.2–9.3%, respectively.^{16–19} In the latest Japanese gastric cancer treatment guidelines (ver. 5), according to complete resection of the primary EGC lesions and possibility of LNM, the NCR is subdivided into eCura C1 and eCura C2 resections.²⁰ Although there have been some studies focused on the relationship between tumor size, location and, ulcer and NCR, few studies explored other pre-procedural endoscopic findings for ESD treatment-related NCR in EGCs, not to mention eCura C1 and eCura C2 resections.^{11,12,21} To minimize the risk of NCR and related unnecessary

additional resection procedures, it is critically important for endoscopists to thoroughly evaluate the risk for NCR before any ESD procedure. The aim of this study was to identify clinically useful risk factors that may predict the risk of NCR, especially of eCura C1 and eCura C2 resections, before the start of an ESD procedure in EGC patients.

Patients and Methods

Patients

We retrospectively reviewed electronic medical records of EGC patients, whose tumors were resected with the ESD procedure between January 2010 and December 2017 at the First Affiliated Hospital of Nanjing Medical University in China. We identified 496 patients for the study. Exclusion criteria were: 1. ESD in stump EGCs (n=7); 2. Synchronous cancers in other organs (n=25); 3. Cases with incomplete clinical or endoscopic data (n=2). As a result, a total of consecutive 463 patients with 472 EGC lesions were included in this observational study (Figure 1).

Due to the retrospective nature of the study, informed consent was waived. The privacy of all the participants was maintained with confidentiality. The study protocol adhered to the ethical principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval no. 2018-SR-234).

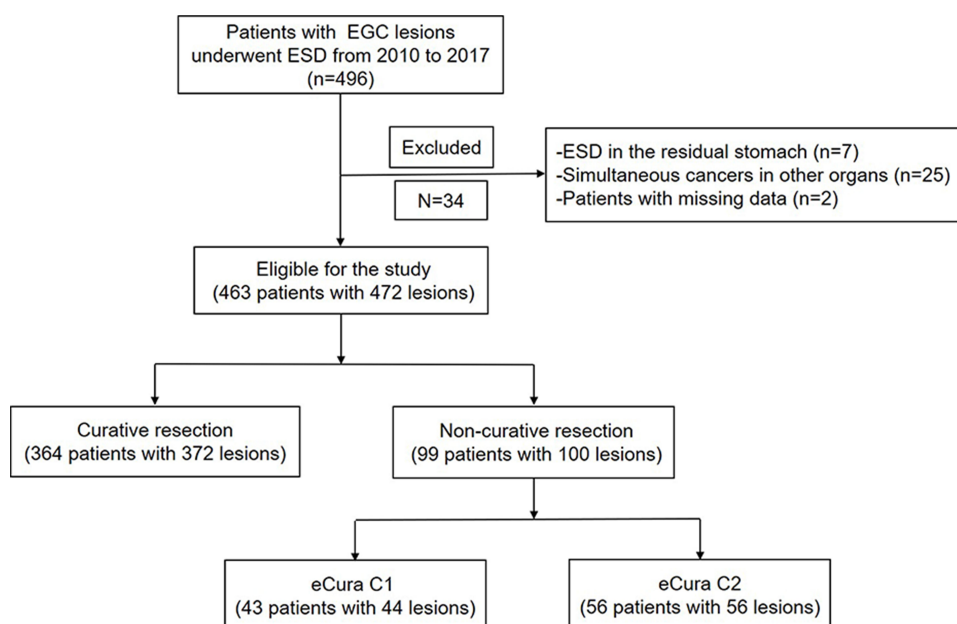


Figure 1 Flow-chart on the study design and patient selection.

Abbreviations: EGC, early gastric carcinoma; ESD, endoscopic submucosal dissection; eCura C1, the only non-curative factor of piecemeal resection or resection en bloc with a positive horizontal margin; eCura C2, the remaining non-curative factors other than eCura C1.

Endoscopic Procedure and Data Extraction

We acquired the clinical data, endoscopic features, and pathological information of the enrolled cases through a review of medical records. The clinical data included age and gender. In each EGC tumor, tumor epicenter location and conventional white light endoscopic features were recorded and tabulated. EGC locations were divided into the cardia-fundus, corpus, angularis, and antrum-pylorus. The tumor circular locations were grouped into the greater curve, lesser curve, anterior wall, and posterior wall. The gross macroscopic features were classified into three major types: elevated (0-I, IIa and IIa + IIc), flat (0-IIb), and depressed (0-IIc, III and IIc + IIa). Also recorded and analyzed were other endoscopic findings, such as ulcer, remarkable redness, uneven surface, margin elevation, enlarged folds, spontaneous bleeding, and negative lifting signs.²²

Pathological Assessment

The tumor maximum microscopic dimension was measured. Resected EGC tumors were histologically categorized into differentiated, undifferentiated, or mixed types. The differentiated type comprised well-moderately differentiated tubular and papillary adenocarcinomas and the undifferentiated type included poorly differentiated adenocarcinoma, poorly cohesive carcinoma/signet-ring cell carcinoma, and mucinous adenocarcinoma. The mixed type contained both differentiated and undifferentiated components. The submucosal infiltration (SM) of EGCs was sub-categorized as SM1 (<500 μ m from the muscularis mucosae) or SM2 (\geq 500 μ m from the muscularis mucosae) subgroups.

Definition of ESD Curative or Non-Curative Resection

Curative ESD resection of tumors was defined as en bloc resection with negative horizontal and vertical margins, without lymphovascular invasion, and fulfilling one of the following conditions: (a) an intramucosal differentiated carcinoma without ulcer, regardless of tumor size; (b) an intramucosal differentiated carcinoma with ulcer, with the size smaller than 30 mm; (c) an intramucosal undifferentiated carcinoma without ulcer, with the size smaller than 20 mm; and (d) a SM1 invasive differentiated carcinoma with the size smaller than 30 mm.²⁰ Otherwise, the ESD resection was classified as NCR, which were sub-categorized as eCura C1 and C2 resections.²⁰ An eCura C1 resection referred to cases only with piecemeal resection or positive horizontal

margins, while an eCura C2 resection was used for cases with other non-curative conditions, such as a positive vertical margin, SM2 or lymphovascular invasion. As for mixed-type carcinomas, the curability was based on that of the predominantly histological type. However, if the undifferentiated carcinoma was not the predominant histological type, an ESD resection for a mixed-type carcinoma with undifferentiated component larger than 20 mm in size or with submucosal invasion was regarded as NCR.²⁰

Long-Term Outcomes After ESD

We estimated the survival based on the number of enrolled EGC patients. All patients were followed up annually or biannually with upper endoscopy after ESD resection to assess tumor recurrence and other pathology. If the medical records were incomplete without required information, a telephonic interview to the patient or the family members was conducted. If the telephone interview failed three times at different time periods, the patient was considered to be lost to follow-up and excluded from statistical analysis. Patient survival was calculated from the date of the first ESD resection procedure for EGCs until the date of death of all causes or the last date of alive at an interview before December 31, 2018.

Statistical Analysis

Data analyses were conducted with R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean \pm standard deviation. The Mann-Whitney *U*-test was used to compare the two groups. Numbers with percentages were used for categorical variables. Univariate and multivariate logistic regression analyses were executed to determine independent risk factors for non-curative, eCura C1 and eCura C2 resections. Survival rates were estimated with the Kaplan-Meier method with a Log rank test. A *P*-value < 0.05 was defined as statistical significance.

Results

Clinical Characteristics

As shown in Figure 1, a total of 472 EGCs from 463 patients were enrolled in the study, which were divided into curative resection (CR) (372 EGCs from 364 patients) and NCR (100 EGCs from 99 patients) groups. In the NCR group, 44 EGCs from 43 patients and 56 EGCs from 56 patients were classified into eCura C1 and C2 groups, respectively. Overall, the percentages of CR, NCR, eCura C1 and C2 were 78.8% (372/472), 21.2% (100/472),

Table 1 Clinicopathologic Features of the Enrolled Early Gastric Carcinomas (Curative Resection Group vs Non-Curative, eCura C1 and eCura C2 Resection Groups, Respectively)

	CR (Lesions) (n=372) (%)	NCR (Lesions) (n=100) (%)	P value	eCura C1 (Lesions) (n=44) (%)	P value	eCura C2 (Lesions) (n=56) (%)	P value
Age (mean \pm SD), years	62.6 \pm 9.2	63.6 \pm 9.8	0.216	63.8 \pm 8.0	0.504	63.4 \pm 11.1	0.306
Gender			0.095		0.631		0.056
Female	97 (26.1%)	18 (18.0%)		10 (22.7%)		8 (14.3%)	
Male	275 (73.9%)	82 (82.0%)		34 (77.3%)		48 (85.7%)	
Tumor size (mean \pm SD), mm	15.1 \pm 6.6	19.1 \pm 7.1	<0.001	17.7 \pm 5.4	<0.001	19.1 \pm 8.1	<0.001
Location - long axis			<0.001		0.009		0.002
Cardia-fundus	115 (30.9%)	55 (55.0%)		24 (54.5%)		31 (55.4%)	
Corpus	34 (9.1%)	8 (8.0%)		2 (4.5%)		6 (10.7%)	
Angularis	86 (23.1%)	17 (17.0%)		10 (22.7%)		7 (12.5%)	
Antrum-pylorus	137 (36.8%)	20 (20.0%)		8 (18.2%)		12 (21.4%)	
Location - short axis			0.386		0.312		0.427
Greater curve	51 (13.7%)	17 (17.0%)		6 (13.6%)		11 (19.6%)	
Lesser curve	185 (49.7%)	40 (40.0%)		9 (20.5%)		5 (8.9%)	
Anterior wall	43 (11.6%)	14 (14.0%)		17 (38.6%)		23 (41.1%)	
Posterior wall	93 (25.0%)	29 (29.0%)		12 (27.3%)		17 (30.4%)	
Gross morphology			0.004		0.64		<0.001
Elevated	173 (46.5%)	38 (38.0%)		19 (43.2%)		19 (33.9%)	
Flat	66 (17.7%)	9 (9.0%)		6 (13.6%)		3 (5.4%)	
Depressed	133 (35.8%)	53 (53.0%)		19 (43.2%)		34 (60.7%)	
Ulceration			0.042		1		0.006
No	327 (87.9%)	80 (80.0%)		39 (88.6%)		41 (73.2%)	
Yes	45 (12.1%)	20 (20.0%)		5 (11.4%)		15 (26.8%)	
Remarkable redness			<0.001		0.003		<0.001
No	330 (88.7%)	72 (72.0%)		32 (72.7%)		40 (71.4%)	
Yes	42 (11.3%)	28 (28.0%)		12 (27.3%)		16 (28.6%)	
Uneven surface			<0.001		0.532		<0.001
No	309 (83.1%)	62 (62.0%)		35 (79.5%)		27 (48.2%)	
Yes	63 (16.9%)	38 (38.0%)		9 (20.5%)		29 (51.8%)	
Margin elevation			<0.001		0.718		<0.001
No	353 (94.9%)	79 (79.0%)		41 (93.2%)		38 (67.9%)	
Yes	19 (5.1%)	21 (21.0%)		3 (6.8%)		18 (32.1%)	
Enlarged folds			0.177		0.327		0.198
No	363 (97.6%)	95 (95.0%)		42 (95.5%)		53 (94.6%)	
Yes	9 (2.4%)	5 (5.0%)		2 (4.5%)		3 (5.4%)	
Spontaneous bleeding			0.002		0.731		<0.001
No	351 (94.4%)	85 (85.0%)		41 (93.2%)		44 (78.6%)	
Yes	21 (5.6%)	15 (15.0%)		3 (6.8%)		12 (21.4%)	
Lifting sign			0.074		0.003		1
Positive	330 (88.7%)	82 (82.0%)		32 (72.7%)		50 (89.3%)	
Negative	42 (11.3%)	18 (18.0%)		12 (27.3%)		6 (10.7%)	

(Continued)

Table 1 (Continued).

	CR (Lesions) (n=372) (%)	NCR (Lesions) (n=100) (%)	P value	eCura C1 (Lesions) (n=44) (%)	P value	eCura C2 (Lesions) (n=56) (%)	P value
Histologic type							
Differentiated	361 (97.0%)	78 (78.0%)	<0.001	40 (90.9%)	0.015	38 (67.9%)	<0.001
Mixed	7 (1.9%)	19 (19.0%)		4 (9.1%)		15 (26.8%)	
Undifferentiated	4 (1.1%)	3 (3.0%)		0 (0.0%)		3 (5.3%)	
Atrophy/intestinal metaplasia							
No	189 (50.8%)	59 (59.0%)	0.145	24 (54.5%)	0.639	35 (62.5%)	0.102
Yes	183 (49.2%)	41 (41.0%)		20 (45.5%)		21 (37.5%)	

Notes: eCura C1, the only non-curative factor of piecemeal resection or resection en bloc with a positive horizontal margin; eCura C2, the remaining non-curative factors other than only piecemeal resection or positive horizontal margins.

Abbreviations: CR, curative resection; NCR, non-curative resection; SD, standard deviation.

9.3% (44/472), and 11.9% (56/472), respectively. As shown in [Table 1](#), age and gender in the CR group were not significantly different from those in the NCR, eCura C1 and eCura C2 groups ($P > 0.05$).

Comparison of Endoscopic Features Between Curative and Non-Curative Groups

From [Table 1](#), the mean tumor size was significantly larger in the NCR, eCura C1 and eCura C2 groups than that in the CR group ($19.1 \pm 7.1\text{mm}$, $17.7 \pm 5.4\text{mm}$, $19.1 \pm 8.1\text{mm}$ vs $15.1 \pm 6.6\text{mm}$, respectively; $P < 0.001$). The most common location of EGC tumors was, in a descending order, the cardia-fundus (36.0%, 170/472), the antrum-pylorus (33.3%, 157/472), angularis (21.8%, 103/472), and corpus (8.9%, 42/472). Tumors located in the cardia-fundus were more common in the NCR (55.0%) group than in the CR group (30.9%) ($P < 0.001$). There were also more tumors located in the cardia-fundus in the eCura C1 and eCura C2 groups ($P < 0.05$). Among various endoscopic findings, in comparison with the CR group, gross morphology, ulcers, remarkable redness, uneven surface, margin elevation, and spontaneous bleeding were significantly more common in the NCR and eCura C2 groups ($P < 0.05$); remarkable redness and negative lifting sign were significantly more common in the eCura C1 group ($P < 0.05$).

Pathologic Features for Non-Curative Resection

As for the final histologic types shown in [Table 1](#), there were more mixed and undifferentiated carcinomas

in the NCR, eCura C1 and eCura C2 groups than in the CR group (22.0%, 10.0%, 32.1% vs 3.0%, respectively), and the differences were significant. ($P < 0.05$). The top three reasons for NCR included horizontal margin involvement ($n = 56$), SM2 invasion ($n = 43$), and vertical margin involvement ($n = 14$) ([Supplementary Table 1](#)).

Predictive Risk Factors for NCR, eCura C1 and eCura C2 Resections

By multivariate logistic regression analyses, we identified significant independent risk factors for NCR as follows: tumor size $>20\text{ mm}$ (Odds Ratio (OR): 2.1, 95% Confidence Interval (CI): 1.2–3.7, $P = 0.015$), tumors located in cardia-fundus (OR: 3.9, 95% CI: 2.2–6.8, $P < 0.001$), uneven surface (OR: 2.0, 95% CI: 1.1–3.7, $P = 0.028$), margin elevation (OR: 2.5, 95% CI: 1.1–5.9, $P = 0.037$), and mixed and undifferentiated types (OR: 9.6, 95% CI: 3.9–23.9, $P < 0.001$) ([Table 2](#)). Significant risk factors for eCura C1 resection included tumors located in cardia-fundus (OR: 2.8, 95% CI: 1.4–5.6, $P = 0.004$), negative lifting sign (OR: 2.8, 95% CI: 1.3–6.1, $P = 0.010$), and mixed and undifferentiated types (OR: 4.0, 95% CI: 1.1–14.5, $P = 0.038$) ([Table 3](#)). Significant risk factors for eCura C2 resection were: tumor size $>20\text{ mm}$ (OR: 2.4, 95% CI: 1.1–5.2, $P = 0.033$), tumors located in cardia-fundus (OR: 6.8, 95% CI: 2.9–15.7, $P < 0.001$), uneven surface (OR: 3.4, 95% CI: 1.6–7.6, $P = 0.002$), margin elevation (OR: 3.6, 95% CI: 1.3–10.1, $P = 0.015$), and mixed and undifferentiated types (OR: 21.5, 95% CI: 5.3–87.2, $P < 0.001$) ([Table 4](#)).

Table 2 Associated Risk Factors with Non-Curative ESD Resection

	Multivariate		
	Odds Ratio	95% Confidence Interval	P-value
Tumor size ≤20mm >20mm	1.0 2.1	(1.2, 3.7)	0.015
Cardia-fundus No Yes	1.0 3.9	(2.2, 6.8)	<0.001
Depressed No Yes	1.0 1.5	(0.9, 2.7)	0.140
Ulceration No Yes	1.0 0.8	(0.4, 1.7)	0.575
Remarkable redness No Yes	1.0 1.7	(0.9, 3.3)	0.086
Uneven surface No Yes	1.0 2.0	(1.1, 3.7)	0.028
Margin elevation No Yes	1.0 2.5	(1.1, 5.9)	0.037
Spontaneous bleeding No Yes	1.0 1.5	(0.6, 3.8)	0.353
Histologic type Differentiated Mixed/ Undifferentiated	1.0 9.6	(3.9, 23.9)	<0.001

Long-Term Outcomes

In this cohort, the average number of follow-up months after ESD resection was 35.7 ± 23.4 (range: 0.0–102.0). The 5-year cancer-specific survival rates were 100.0%, 87.5%, 91.1% and 82.1% in the CR, NCR, eCura C1, and eCura C2 groups, respectively. The 5-year cancer-specific survival rate was significantly worse for patients in the NCR group than for those in the CR group ($P < 0.0001$) (Figure 2A). In the subgroup analysis, there were no significant differences in the cancer-specific survival

Table 3 Associated Factors with eCura C1 Resection of ESD

	Multivariate		
	Odds Ratio	95% Confidence Interval	P-value
Tumor size ≤20mm >20mm	1.0 2.1	(1.0, 4.5)	0.057
Cardia-fundus No Yes	1.0 2.8	(1.4, 5.6)	0.004
Remarkable redness No Yes	1.0 1.7	(0.7, 3.9)	0.182
Lifting sign Positive Negative	1.0 2.8	(1.3, 6.1)	0.010
Histologic type Differentiated Mixed/ Undifferentiated	1.0 4.0	(1.1, 14.5)	0.038

rate between the eCura C1 and C2 groups ($P = 0.82$) (Figure 2B), and compared to patients without additional surgery after non-curative ESD resection, the cancer-specific survival rate of patients with additional surgery was significantly better ($P = 0.033$) (Figure 2C). The 3- and 5-year cancer-free survival rates were 97.1% and 95.3%, and 85.8% and 83.4% in the CR and NCR groups, respectively. The 5-year cancer-free survival rate was significantly lower for patients in the NCR group than for those in the CR group ($P < 0.0001$) (Figure 3).

Discussion

ESD has been recognized as a preferred treatment for EGCs, but is not a perfect technique because of a high prevalence of NCR.¹⁵ In our cohort, the rates of NCR, eCura C1 and eCura C2 were 21.2%, 9.3%, and 11.9%, respectively, which are similar to those reported by others in recent studies.^{11,12,23} Our results showed that tumor size >20 mm, tumors location in cardia-fundus, uneven surface, margin elevation, and mixed and undifferentiated types were closely associated with a high risk for NCR, in particular for eCura C2 resection, while the risks for the

Table 4 Associated Factors with eCura C2 Resection of ESD

	Multivariate		
	Odds Ratio	95% Confidence Interval	P-value
Tumor size			
≤20mm	1.0		
>20mm	2.4	(1.1, 5.2)	0.033
Cardia-fundus			
No	1.0		
Yes	6.8	(2.9, 15.7)	<0.001
Depressed			
No	1.0		
Yes	1.6	(0.7, 3.6)	0.219
Ulceration			
No	1.0		
Yes	1.0	(0.4, 2.5)	0.979
Remarkable redness			
No	1.0		
Yes	2.0	(0.9, 4.5)	0.092
Uneven surface			
No	1.0		
Yes	3.4	(1.6, 7.6)	0.002
Margin elevation			
No	1.0		
Yes	3.6	(1.3, 10.1)	0.015
Spontaneous bleeding			
No	1.0		
Yes	2.3	(0.8, 6.8)	0.133
Histologic type			
Differentiated	1.0		
Mixed/ Undifferentiated	21.5	(5.3, 87.2)	<0.001

eCura C1 resection included tumors located in cardia-fundus, negative lifting sign, and mixed and undifferentiated carcinomas. As expected, the 5-year cancer-specific survival and cancer-free survival rates were better in the CR group than those in the NCR group, and the patients with additional surgery after non-curative ESD resection had better cancer-specific survival than those without additional surgery.

In this study, although the lesion size was measured based on pathologic tissue of ESD, we could use

instruments to make a general assessment in preoperative endoscopic examination. Therefore, it can also provide some reference significance for endoscopists. Large tumors and proximal gastric location of EGCs have been reported as risk factors for non-curative ESD resection,^{11,12,21,23,24} which are confirmed in our cohort. In this cohort, the results demonstrated large tumors were more likely to contain undifferentiated carcinoma components. Therefore, we found large tumor size was prone to deep submucosal invasion and positive margins ([Supplementary Table 2](#)). The wall and submucosa of the cardia and fundus are thinner than those of other parts. Moreover, small lymphatic capillaries directly exist above the mucosal muscularis; and the cardia and fundus are difficult anatomical positions for endoscopic manipulation.²⁵ As a result, in our study, tumors located in the cardia-fundus were more vulnerable to occurring deep submucosal invasion and positive margins ([Supplementary Table 2](#)).

For ESD resection of EGCs, our study also disclosed other endoscopic findings for NCR. Regarding to eCura C2 resection, uneven surface and margin elevation, that is to say, tumor nodularity, and a protruding edge surrounding a tumor, were independent risk factors. Abe et al considered tumors with these signs alluded potentially deep invasion.²⁶ In the present study, the results revealed uneven surface and margin elevation were correlated with deep submucosal invasion, positive vertical margins and lymphovascular invasion. What's more, a greater proportion of mixed and undifferentiated EGCs had these features than differentiated EGCs ([Supplementary Table 2](#)). Interestingly, negative lifting sign was a risk factor for eCura C1 resection, but not for eCura C2 resection. Negative lifting sign is usually due to scar formation at the bottom of an ulcer, or fibrosis due to tumor infiltration to the submucosa with desmoplastic reaction. In our cohort, negative lifting sign was tendentiously associated with piecemeal resection, and had a relationship to positive horizontal margins ([Supplementary Table 2](#)). Although reported as one of significant risk factors for the NCR by others,^{11,23,24} ulceration was not a significant risk factor for NCR in our cohort. However, we found tumors with ulcers had a correlation with positive vertical margins ([Supplementary Table 2](#)).

Mixed and undifferentiated EGC tumors have been shown to be risk factors of NCR,^{12,27,28} which parallel to

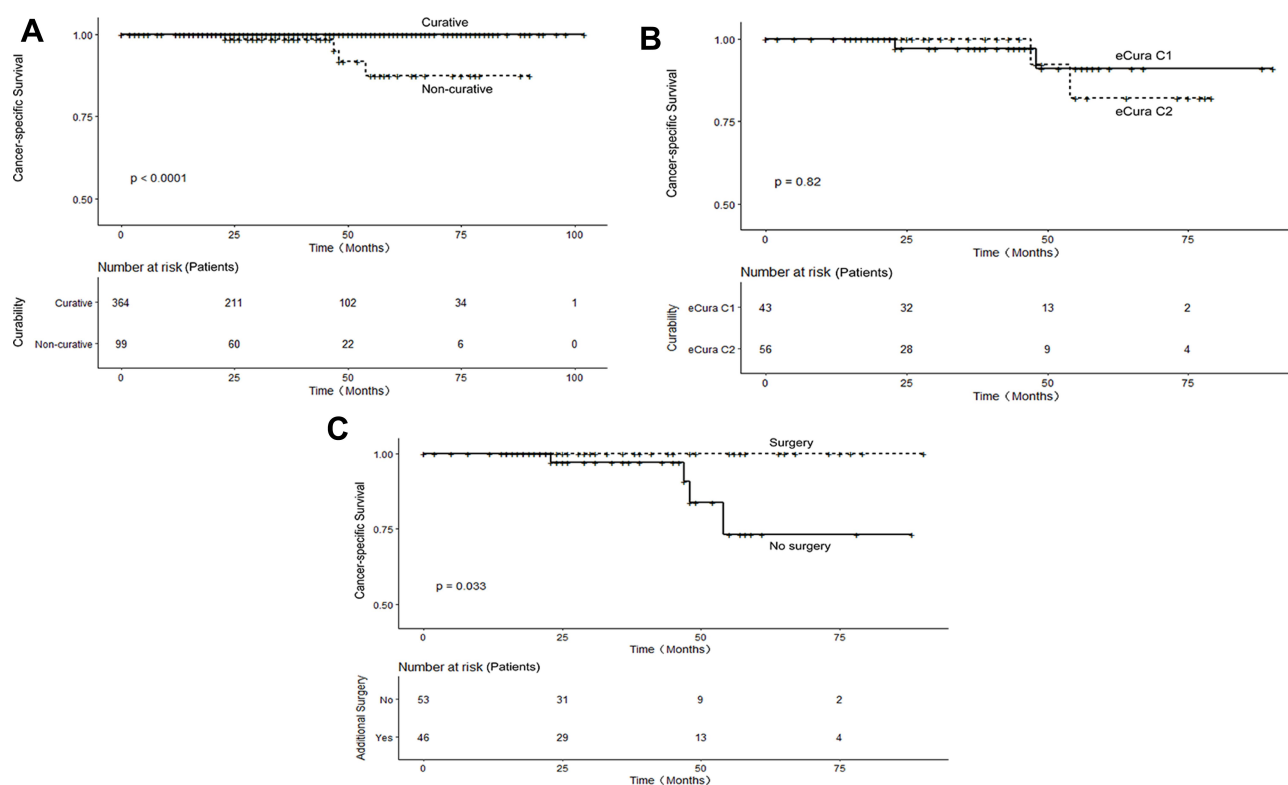


Figure 2 Cancer-specific survival for the patients. **(A)** Cancer-specific survival for the patients in the curative and non-curative resection groups. **(B)** Cancer-specific survival for the patients in the eCura C1 and C2 resection groups. **(C)** Cancer-specific survival for the patients with and without additional surgery after non-curative resection. **Abbreviations:** eCura C1, the only non-curative factor of piecemeal resection or resection en bloc with a positive horizontal margin; eCura C2, the remaining non-curative factors other than eCura C1.

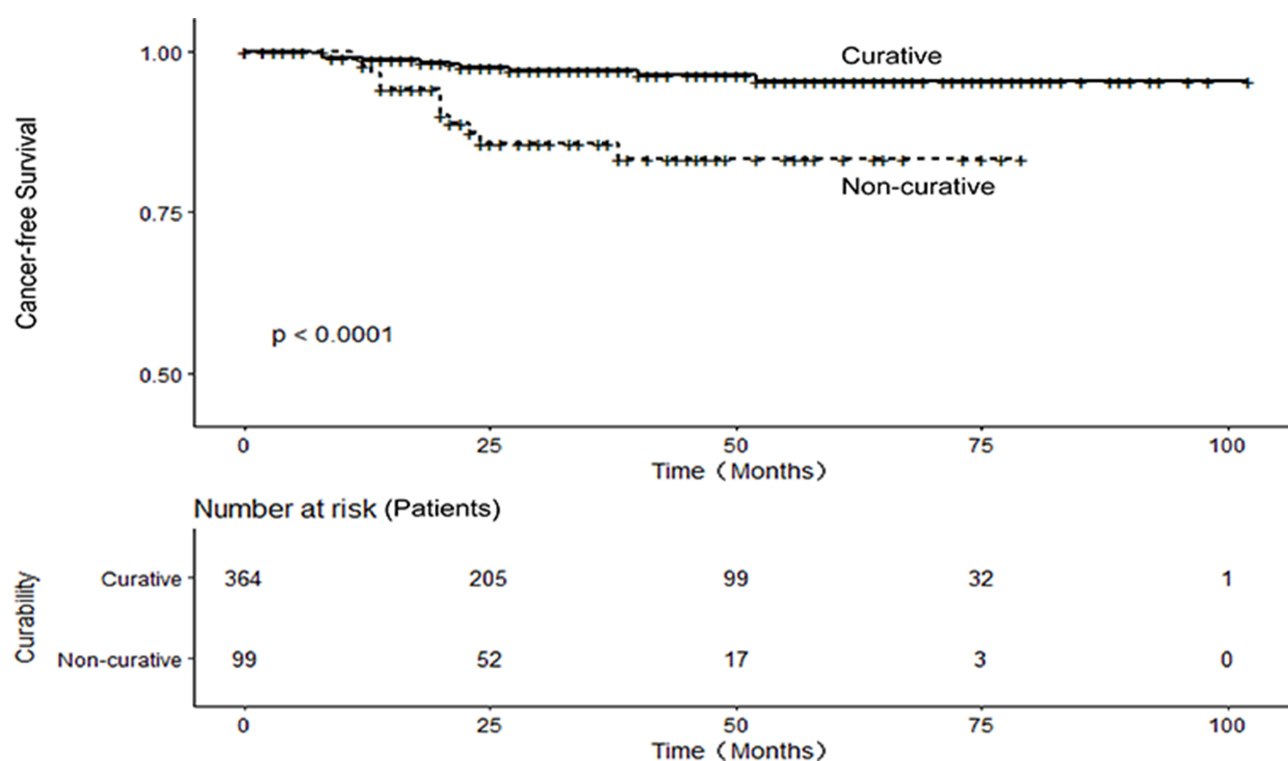


Figure 3 Cancer-free survival for the patients in the curative and non-curative resection groups.

our results. In this study, mixed and undifferentiated EGC tumors were relevant to deep submucosal invasion, positive margins and lymphovascular invasion ([Supplementary Table 2](#)). Undifferentiated EGCs are more prone to deep infiltration, and intramucosal spreading over a large area; therefore, the actual tumor size in resection specimens is often larger than the assumed size under endoscopy.^{29,30} The pre-ESD diagnosis of mixed EGCs was difficult and there is no unified standard. As previously reported, mixed and undifferentiated EGCs diagnosed at the final ESD resection specimens were most frequently misdiagnosed as differentiated EGCs at initial biopsies.¹² If the pre-ESD biopsy showed differentiated EGCs, but the possibility of suspected undifferentiated components was observed, the mixed type should be highly suspected, and the endoscopists should be on the alert for the possibility of NCR.

The prognosis of EGC patients after ESD resection is excellent, as also shown in our cohort with the 3- and 5-year cancer-specific survival rates in the CR group over 99%.³¹ As expected, in comparison with the CR group, the 5-year survival rate was lower in NCR, eCura C1, and eCura C2 groups. Local recurrence along with possible nodal metastasis remain the causes of poor prognosis.^{10,19,32} Previous studies have shown that additional surgery after NCR can lead to a better prognosis for the patients with NCR.^{10,18,33,34} From our study, we also found higher cancer-specific survival rate for the patients with additional surgery than for those without additional surgery. Despite the risks associated with surgical procedures, additional surgery may result in better long-term outcomes. Local recurrence was found in patients with curative ESD resection, but as long as treated timely, they would have good prognosis. Therefore, regular surveillance is still necessary for patients after CR.

There are several major limitations for this observational study. First, this was a retrospective study at a single academic referral center. A selection bias might exist. However, we collected consecutive cases after a strict selection process, which minimized potential selection bias, if any. Second, endoscopic appearances of all EGC tumors were recorded as still images for this study, which might not be enough to demonstrate all aspects of an EGC tumor. In reality, still images of EGCs remain the most common materials for this type of clinical study. We look forward to adopting more advanced endoscopy technology to improve the EGC endoscopic study quality. Despite of these limitations, we believe our results are solid and helpful to digestive endoscopists dealing with EGCs in

their clinical practice. Further studies are warranted to verify our preliminary findings.

Conclusion

We identified various endoscopic and pathologic features of EGCs to predict non-curative resection, especially eCura C1 and eCura C2 resections before ESD. These clinically valuable factors would be very informative to endoscopists and surgeons who perform ESD to resect EGCs.

Abbreviations

EGC, early gastric carcinoma; LNM, lymph node metastasis; ESD, endoscopic submucosal dissection; NCR, non-curative resection; SM, submucosal infiltration; CR, curative resection; OR, odds ratio; CI, confidence interval.

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Disclosure

The authors declare no conflict of interests for this article.

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