Clinical significance of additional gastrectomy after non-curative endoscopic submucosal dissection for early gastric cancer: a retrospective single-center study

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Purpose: Additional surgery is recommended for patients after a non-curative endoscopic submucosal dissection (ESD) to prevent residual cancer (RC) or lymph node metastasis (LNM). We aimed to evaluate the clinicopathologic characteristics of patients who underwent an additional gastrectomy after a non-curative ESD procedure and identify the risk factors of RC and LNM.

Methods: We retrospectively assessed the clinicopathological factors of 73 patients who underwent additional gastrectomy following a non-curative ESD between January 2009 and December 2019 at our center.

Results: RC and LNM rates after additional gastrectomy were 9.6% and 8.2%, respectively. Invasion deeper than 500 μ m ($P=0.045$), positive horizontal resection margin ($P<0.001$), and positive ESD margin ($P=0.001$) were identified as statistically significant factors in univariate analysis for RC, but not in multivariate analysis. Lymphatic invasion was the only risk factor found to be significant in both univariate and multivariate analyses ($P=0.005$ and $P=0.012$).

Conclusion: Additional gastrectomy is necessary to prevent RC or LNM after non-curative ESD. Lymphatic invasion was also associated with LNM in patients who underwent an additional gastrectomy after a non-curative ESD, and in such cases, active treatment is required.

Keywords: Endoscopic submucosal dissection, Gastric cancer, Lymph node metastasis, Gastrectomy, Residual cancer

INTRODUCTION

Gastric cancer is the most common cancer and the fourth leading cause of cancer-related deaths in South Korea [1]. Early gastric cancer (EGC) is defined as adenocarcinoma confined to the mucosa or submucosa of the stomach with or without regional lymph node metastasis (LNM), and the prognosis is excellent even in the

presence of LNM [2].

The standard treatment option for gastric cancer is gastrectomy with regional lymph node dissection. However, in Korea and Japan, endoscopic submucosal dissection (ESD) has been accepted as an optional treatment for EGC without LNM [3]. The absolute indication for ESD as recommended by the Japanese gastric cancer treatment guidelines 2014 (4th edition) includes a differentiated type of adenocarcinoma without ulceration, the depth of invasion of which is clinical T1a and the diameter is ≤ 2 cm [4].

For patients who underwent non-curative ESD, additional surgery is recommended to prevent residual cancer (RC) or LNM. Non-curative factors include submucosal invasion (SM1) > 500 μ m, lymphovascular invasion, undifferentiated histology, large tumor size, and a positive resection margin [5].

In this study, we aimed to evaluate the clinicopathological characteristics of patients who underwent an additional gastrectomy after a non-curative ESD procedure to identify the risk factors of RC and LNM.

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METHODS

Patients

We retrospectively reviewed 73 patients who underwent additional gastrectomy after non-curative ESD procedures between January 2009 and December 2019 at our center. The indication for ESD was decided according to the recommendations laid out by the Korean Practice Guidelines for Gastric Cancer (2018) for endoscopic resection [6]. Additional gastrectomy after ESD was performed in cases in which the pathologic result was beyond the criteria of curative resection, lymphatic invasion, or positive resection margins.

The study was approved by the Institutional Review Board of Konkuk University Medical Center (IRB No. KUMC 2021-09-002) and performed in accordance with the principles of the Declaration of Helsinki. The informed consent was waived because this study design is a retrospective review.

Procedure

Additional gastrectomy was performed on 73 patients with D1+ lymph node dissection after non-curative ESD.

Definitions

Criteria for curative resection was defined according to the following four grades: (1) differentiated (well or moderately differentiated tubular or papillary) mucosal cancer measuring > 2 cm in the long diameter without ulcer (active or scar); (2) differentiated mucosal cancer measuring < 3 cm with ulcer; (3) undifferentiated mucosal cancer measuring < 3 cm without ulcer; or (4) differentiated submucosal cancer measuring < 3 cm with subtle submucosal invasion (< 500 μ m).

Statistical analysis

IBM SPSS Statistics version 17 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For categorical variables, the chi-square test or Fisher exact test was used. Based on this, a univariate analysis was performed. Multivariate logistic regression analysis was used to identify risk factors for RC and LNM, and a $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics

During the study period, 73 patients (mean age, 62.2 ± 9.9 years) underwent additional gastrectomy after non-curative ESD for EGC. The tumor size was 2.1 cm (range, 0.5–5.7 cm) and 16.4% of that exceeded 3 cm (Table 1). The reasons for additional gastrecto-

Table 1. Clinicopathologic characteristics

Characteristic	Value (n = 73)
Age (yr)	62.2 $\pm$ 9.9 (31–77)
Sex	
Male	54 (74.0)
Female	19 (26.0)
Location of tumor	
Upper	8 (11.0)
Middle	17 (23.3)
Lower	48 (65.7)
Tumor type	
Elevated	23 (31.5)
Flat	14 (19.2)
Depressed	36 (49.3)
Type of surgery	
Distal gastrectomy	59 (70.9)
Pylorus preserving gastrectomy	1 (1.4)
Total gastrectomy	13 (17.8)
Tumor size (cm)	2.1 $\pm$ 1.1 (0.5–5.7)
< 2	41 (56.2)
2 to < 3	20 (27.4)
$\geq$ 3	12 (16.4)
Depth of tumor	
Mucosa	20 (27.4)
SM1	14 (19.2)
$\geq$ SM2	39 (53.4)
Tumor differentiation	
Differentiated type	55 (75.3)
Undifferentiated type	18 (24.7)
Ulceration	43 (58.9)
Resection margin positive	30 (41.1)
Horizontal margin positive	16 (21.9)
Vertical margin positive	16 (21.9)
Lymphatic invasion	20 (27.4)

Values are presented mean $\pm$ standard deviation (range) or number (%). SM, submucosa.

my included submucosal invasion deeper than SM2 in 39 cases, ulceration in 43 cases, undifferentiated type in 18 cases, positive margin in 30 cases (horizontal 16 and vertical 16), and lymphatic invasion in 20 cases.

Characteristics of cases with or without RC

The clinicopathological features of the patients with or without RC after additional gastrectomy are shown in Table 2. RC was detected in 9.6% of the cases (7/73). The ESD margin included horizontal and vertical resection margins. Univariate analysis determined that invasion deeper than SM2 ($P = 0.045$), horizontal resection margin positivity ($P < 0.001$), and ESD margin positivity ($P = 0.001$) were

Table 2. Characteristics of cases with and without residual cancer

Characteristic	Residual cancer, No. (%)		P-value
	Yes (n = 7)	No (n = 66)	
Age			0.430
< 65 yr	5 (13.5)	32 (86.5)	
≥ 65 yr	2 (5.6)	34 (94.4)	
Sex			0.668
Male	6 (11.1)	48 (88.9)	
Female	1 (5.3)	18 (94.7)	
Location of tumor			0.720
Upper	1 (12.5)	7 (87.5)	
Middle	2 (12.5)	16 (87.5)	
Lower	4 (8.3)	43 (91.7)	
Tumor size			0.124
< 3 cm	4 (6.8)	55 (93.2)	
≥ 3 cm	3 (21.4)	11 (78.6)	
Depth			0.045
< SM2	6 (17.6)	28 (82.4)	
≥ SM2	1 (2.6)	38 (97.4)	
Differentiation			0.673
Differentiated	6 (10.9)	49 (89.1)	
Undifferentiated	1 (5.6)	17 (94.4)	
Macroscopic type			0.430
Non-depressed	5 (13.5)	32 (86.5)	
Depressed	2 (5.6)	34 (94.4)	
Vertical margin			1.000
Positive	1 (6.2)	15 (93.8)	
Negative	6 (10.7)	51 (89.3)	
Horizontal margin			< 0.001
Positive	7 (43.8)	9 (56.2)	
Negative	0	57 (100)	
ESD margin			0.001
Positive	7 (23.3)	23 (76.7)	
Negative	0	43 (100)	
Ulceration			0.435
Yes	3 (7.0)	40 (93.0)	
No	4 (13.3)	26 (86.7)	
Lymphatic invasion			0.665
Yes	1 (5.0)	19 (95.0)	
No	6 (11.3)	47 (88.7)	

SM, submucosa; ESD, endoscopic submucosal dissection.

significant factors for RC. However, multivariate logistic regression analysis did not identify these as being statistically significant factors.

Characteristics of cases with or without LNM

The relationships between the clinicopathological characteristics and LNM after additional gastrectomy are summarized in Table 3.

Table 3. Characteristics of cases with and without lymph node metastasis

Characteristic	Lymph node metastasis, No. (%)		P-value
	Yes (n = 6)	No (n = 67)	
Age			0.107
< 65 yr	1 (2.7)	36 (97.3)	
≥ 65 yr	5 (13.9)	31 (86.1)	
Sex			1.000
Male	5 (9.3)	49 (91.7)	
Female	1 (5.3)	18 (94.7)	
Location of tumor			0.527
Upper	1 (12.5)	7 (87.5)	
Middle	2 (11.1)	16 (88.9)	
Lower	3 (6.4)	44 (93.6)	
Tumor size			0.080
< 3 cm	3 (5.1)	56 (94.9)	
≥ 3 cm	3 (21.4)	11 (78.6)	
Depth			0.206
< SM2	1 (2.9)	33 (97.1)	
≥ SM2	5 (12.8)	34 (87.2)	
Differentiation			1.000
Differentiated	5 (9.1)	50 (90.9)	
Undifferentiated	1 (5.6)	17 (94.4)	
Macroscopic type			0.674
Not-depressed	4 (10.8)	33 (89.2)	
Depressed	2 (5.6)	34 (94.4)	
Vertical margin			0.606
Positive	2 (12.5)	14 (87.5)	
Negative	4 (7.0)	53 (93.0)	
Horizontal margin			0.328
Positive	0	16 (100)	
Negative	6 (10.5)	51 (89.5)	
ESD margin			1.000
Yes	2 (6.7)	28 (93.3)	
No	4 (9.3)	39 (90.7)	
Ulceration			0.221
Yes	2 (4.7)	41 (95.3)	
No	4 (13.3)	26 (86.7)	
Lymphatic invasion			0.005
Yes	5 (25.0)	15 (75.0)	
No	1 (1.9)	52 (98.1)	

SM, submucosal; ESD, endoscopic submucosal dissection.

LNM was found in six of the 73 patients (8.2%) who underwent additional gastrectomy. Lymphatic invasion was the only significant factor for LNM ($P = 0.005$), and logistic regression analysis showed statistical significance ($P = 0.012$). However, cases with tumors < 3 cm were 5.1% and cases with tumors ≥ 3 cm were 21.4%, tumor size was weakly associated with LNM ($P = 0.080$), but other factors were not statistically significant (Table 3).

DISCUSSION

ESD is a minimally invasive procedure performed for the treatment of EGC. Compared to surgery, ESD can avoid side-effects such as appetite loss, dysphagia, eating restrictions, and anxiety [7]. However, Tanabe et al. [8] reported a local recurrence rate of 0.22% in the absolute indication group for ESD, and local recurrence and LNM rates were 1.26% and 0.14% in the expanded indication group. They mentioned that local recurrence can occur when curative resection is not achieved at the horizontal or vertical margin, and LNM is associated with the presence of risk factors such as submucosal microinvasion and lymphovascular invasion.

Toyokawa et al. [9] reported that among patients who underwent non-curative ESD without additional gastrectomy, the incidence rates of RC and LNM were 9% and 9%, respectively. Lymphovascular invasion and the presence of undifferentiated type tumors were identified as risk factors for LNM, and a positive horizontal margin was identified as a risk factor for RC. Choi et al. [10] reported recurrence in 15% (3/20) of patients with SM2 gastric cancer who were followed up after ESD without surgery. In both studies, the authors strongly recommended additional gastrectomy for patients that underwent non-curative ESD.

In our study, the rate of RC was 9.6% (7/73). The depth of invasion ($\geq$ SM2), positive horizontal margin, and ESD margin were associated with RC in the univariate analysis ($P = 0.045$, $P < 0.001$, and $P = 0.001$). However, these factors were not statistically significant in the multivariate analysis. In previous studies of patients who underwent additional gastrectomy after ESD, RC rates ranged from 7.7% to 22.2%. Positive horizontal margin, positive vertical margin, ulceration, lymphatic invasion, and neural invasion were reported as risk factors for RC [11-14]. In our cases, RC did not exist in the negative horizontal margin. However, Park et al. [15] reported the possibility of remnant malignant cells remaining on the negative resection margin because the coagulated portion of the resection margin could not be assessed accurately. In addition, RC may be considered to be cancer cells that spilled out from the vessels due to vascular stasis [9].

LNM rates for patients who underwent additional gastrectomy after non-curative ESD ranged from 7.5% to 17.8% [12-14,16]. Depth of invasion, lymphatic invasion, vascular invasion, and differentiation were the associated risk factors for LNM [12,13,16]. In our study, the LNM rate after additional gastrectomy was 8.2% (6/73), and lymphatic invasion was the only risk factor for LNM ($P = 0.012$). Yamao et al. [17] reported that lymphatic invasion is an independent risk factor for LNM. Furthermore, Kamata et al. [18] demonstrated that matrix metalloproteinase-1 secreted from gastric cancer cells plays an important role in LNM as a sequela of

lymphatic invasion.

There are some limitations to our study. This study was conducted retrospectively at a single institution. Because the number of cases included in this study was small, the evidence regarding the risk factors identified in this study is insufficient. Further multicenter data and prospective studies will be able to validate our findings and establish the risk factors definitively.

In conclusion, additional gastrectomy is necessary to prevent RC or LNM after non-curative ESD. Lymphatic invasion was also associated with LNM in patients who underwent an additional gastrectomy after a non-curative ESD, and in such cases, active treatment is required.

CONFLICT OF INTEREST

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

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