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Original Article

Long-term Outcomes of Patients With Early Gastric Cancer Who Had Lateral Resection Margin-Positive Tumors Based on Pathology Following Endoscopic Submucosal Dissection

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ABSTRACT

Purpose: Long-term outcomes of patients with positive lateral margins (pLMs) after endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). This study aimed to evaluate the remnant cancer and survival rates of patients with pLMs compared with those who underwent curative resection.
Materials and Methods: A retrospective analysis was performed on consecutive patients with pLMs as the only non-curative factor of expanded indication who underwent ESD for EGC with a follow-up duration of 5 years or more. The rates of remnant cancer, recurrence, and survival were analyzed and compared to those of control patients who underwent curative resection by propensity score matching.
Results: Among 3,515 patients treated with ESD between 2005 and 2018, 123 non-curative EGCs were retrospectively analyzed. A total of 108 patients were followed up without endoscopic or surgical resection for 8.2 years. The control group was matched in a 1:1 ratio with patients with EGC who underwent curative resection after ESD. The observation group with pLMs had a higher incidence of remnant cancer (25.9%; 28/108) compared to that in the curative resection group (0/108; P=0.000). The remaining tumors were treated with surgical or endoscopic resection, and no additional recurrences were observed. The overall survival analysis demonstrated no significant difference between the observation and curative resection groups (P=0.577).
Conclusions: No difference was observed in the overall survival rate between observation and curative resection groups. Therefore, observation may be a possible option for incomplete ESD with pLMs if continuous follow-up is performed.

Keywords: Gastric cancer; Endoscopic submucosal dissection; Margins of excision

INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely used in the treatment of early gastric cancer (EGC). Further treatment is recommended if a curative resection cannot be achieved after ESD [1, 2]. However, the risk of lymph node metastasis is low when the only non-

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study design, analysis, interpretation of the data, drafting of the article, critical revision of the article, and final approval for submission of the article.

Conflict of Interest

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

Author Contributions

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curative factor is positive lateral margins (pLMs) [3]. Therefore, surgery and endoscopic treatments such as additional ESD and argon plasma coagulation (APC) are widely practiced in these cases. Moreover, in some cases, close follow-up without further treatment is required [4]. However, few studies report the long-term prognosis. A recent study by Kim et al. [5] published the long-term follow-up results of patients who underwent ESD or APC after pLMs; however, the study was limited to cases with additional endoscopic treatment. In this study, we examined the long-term prognosis of patients with pLMs as the only non-curative factor, with a long-term duration of at least 5 years. Particularly, we examined the long-term prognosis of patients who were followed up after pLMs.

MATERIALS AND METHODS

Study population and data collection

We retrospectively analyzed patients who underwent ESD for EGC at Seoul National University Hospital, a single tertiary institution. Patients who underwent the procedure between January 1, 2005, and December 31, 2017, with a minimum follow-up of 5 years, were included. As a control group, we enrolled patients who underwent ESD during the same period and achieved complete resection. They were matched in a 1:1 ratio through propensity score matching with the observation group. Furthermore, the R 3.6.2 statistical program was used for the propensity score matching. ESD was performed using electrosurgical IT knives (KD-610L and KD-611Ll; Olympus, Tokyo, Japan), dual knives (KD-650Q; Olympus), or both. Curative resection of ESD was based on a post-procedural pathology report published by the Korean Practice Guidelines for Gastric Cancer [6]. The expanded indication of criteria for a curative resection consists of 4 conditions [7]: 1) en-bloc resection of the lesion; 2) either of four possibilities i) predominantly differentiated pT1a lesions ≥2 cm in diameter without ulceration, ii) predominantly differentiated pT1a lesions <3 cm in diameter with ulceration, iii) predominantly undifferentiated pT1a lesions <2 cm in diameter without ulceration, or iv) predominantly differentiated pT1b lesions <3 cm in diameter with submucosal invasion <500 μm from muscularis mucosa (SM1); 3) no lymphatic or vascular invasion; and 4) negative lateral and vertical margin. Among them, we enrolled patients with a pLM as the only non-curative resection factor. The invaded margin was categorized as single if it invaded only one unilateral direction out of four directions, and multiple if it invaded two or more directions. Experienced endoscopists performed ESD using standardized techniques and instruments. After ESD, the specimens were serially sectioned at 2-mm intervals and evaluated for tumor involvement in four lateral directions (distal, proximal, anterior, and posterior) and the vertical direction. A detailed description of the ESD procedures and histopathological evaluation performed at our institution has been presented elsewhere [8].

Determination of future treatment policy

A three-step procedure was employed to determine follow-up after ESD. Immediately after ESD, the endoscopist performed a visual observation while fixing the specimen. The extent to which the cauterization effect was applied to the edge of the specimen and the degree of shrinkage of the specimen were evaluated to verify the achievement of complete success. Second, all experienced faculty members of the upper gastrointestinal department reviewed the case and determined appropriate follow-up actions. In certain instances, when deciding the second stage proved challenging, future actions were determined following a discussion with a pathologist. If additional surgical treatment was selected, radical gastrectomy was performed. To ensure sufficient resection margins, the extent of gastrectomy was determined

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by the location of the tumor removed using ESD. Partial gastrectomy with pylorus-sparing surgery was performed for lesions located in the lower two-thirds of the stomach. However, total or proximal gastrectomy was performed for proximal gastric cancer. In a limited number of cases, pylorus-preserving gastrectomy was carried out. All surgical procedures were based on standard gastrectomy rather than sentinel lymph node navigation surgery [9]. According to the 2022 Korean guidelines for gastric cancer, the extent of lymph node resection was determined as either D1+ or D2 resection [6]. If endoscopic treatment was selected as an additional treatment, the attending physician evaluated the clinicopathological factors and determined the treatment strategy between APC and ESD. Subsequent ESD and histopathological evaluations were performed in the same manner as initial ESD. When the APC was selected, the target lesion was ablated until the surface appeared greyish-brown and sufficiently dry. The APC mode was set to VIO 300 D (Erbe Elektromedizin GmbH, Tuebingen, Germany) with an argon gas flow rate of 1.8 L/min. The pulse coagulation mode was utilized with an effect level set to 2, and a power output of 40 W [10]. The resected specimen was extended immediately and fixed with pins on a polystyrene board to prevent the rolling of the edges. Subsequently, the sample was fixed in 10% formalin. The gross specimen was placed on a piece of mapping paper with grid lines and scanned to indicate its boundaries. The total length (mm) of the involved lateral resection margin was calculated by adding the number of horizontal and vertical grid lines where the tumor was located on the mapping paper.

Follow-up after treatment

Patients underwent upper endoscopy 3–6 months after the ESD or surgery. After the initial treatment, patients were advised to undergo follow-up appointments every 6–12 months, during which abdominal computed tomography and endoscopy were recommended for at least 5 years. The group that opted for observation after the first ESD underwent a close follow-up. A follow-up gastroscopy was performed 3 months after ESD. Additionally, gastroscopy and computed tomography were performed at 6-month intervals for 2 years, and then annually for 5 years. During each gastroscopy, the ESD site was closely examined by a specialized endoscopist using white light and narrow band imaging, and biopsies were performed if necessary. Additionally, abdominal computed tomography and blood tests, including those for cancer markers, were performed when deemed necessary. The follow-up duration was defined as the period from the date of non-curative ESD to the last date of the diagnostic test confirmed in the medical record. Recurrence was classified as local, metachronous, regional, or distant lymph node involvement. Local recurrence was defined as the diagnosis of cancer at the ESD site or the anastomosis site following surgery. Metachronous recurrence was defined as the detection of cancer distant from the site of ESD or the anastomosis site at least 1 year after resection. Synchronous cancer was defined as the detection of cancer within 1 year [11]. Lymph node recurrence was defined as cancer recurrence in a regional lymph node within the surgical field for gastric cancer as identified by computed tomography and/or subsequently confirmed by biopsy or surgical dissection. Distant recurrence was defined as cancer recurrence in a lymph node beyond the surgical field and/or other organs, which was detected by computed tomography and pathological examination. Recurrence-free survival was defined as the time between the date of initial ESD and the date of diagnosis of recurrence of any kind (local, metachronous, lymph node, or distant). Extra-gastric recurrence-free survival was defined as the duration spanning from the date of initial treatment to the date of detection of lymph node or distant recurrence. Overall survival was defined as the period from the date of initial treatment to the date of death from any cause or the date of censoring. To obtain the status and date of death for survival analysis, we required information from a government agency called the Ministry of the Interior and

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Safety of Korea, which utilized the social security numbers of the enrolled patients. Patients with no reported deaths by the screening date (August 31, 2023) were excluded. This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital. (IRB number 2210-080-1368), and the need for informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

We compared survival rates and incidence of remnant cancer between the observation and propensity-matched complete resection groups. Nine variables were used in propensity score matching (patient sex, age, number of ESD performed, tumor location, tumor pathology type, Lauren classification, tumor size, tumor depth of invasion, and *Helicobacter Pylori* infection status). Survival curves were plotted using the Kaplan–Meier method, and differences in survival between groups were assessed using the log-rank test. The incidence rate of remnant cancer and survival analyses were performed using SPSS 27.0 (SPSS; IBM Corp., Armonk, NY, USA).

RESULTS

Demographics and clinicopathologic characteristics

Between 2005 and 2017, 3,515 patients underwent ESD for 4,181 EGCs. Of the patients with pLMs as the only non-therapeutic component, a total of 123 patients were followed up for more than 5 years. Approximately, 108 patients (87.8%) were monitored without immediate treatment. Thirteen patients (10.6%) underwent surgical treatment, meanwhile, two patients (1.6%) were treated endoscopically. The characteristics of each group are presented in **Table 1**. The involved lateral margin was significantly longer in the patient group who underwent surgery immediately after the initial ESD than in the observation group (P<0.05). No statistically significant differences were observed in the other areas.

Comparison of clinicopathological characteristics between the observation group with pLMs and 1:1 matched curative resection group

Of the 108 patients who were followed up (median 80.8 [2.9–223.6] months), 28 (25.9%) developed remnant cancer during follow-up. Similarly, 108 patients who underwent complete resection were matched in a 1:1 ratio using a propensity score from the same duration. **Table 2** summarizes the characteristics of the patients in the curative resection, pLMs with remnant cancer, and pLM without remnant cancer groups. The curative resection and observation groups with pLMs that underwent 1:1 propensity matching demonstrated a difference in tumor size (P<0.05), but no differences were observed in other aspects.

Extra-gastric metastases case

Among all the patients, one had confirmed extra-gastric metastases (**Table 3**). The patient underwent ESD; however, pathological examination confirmed residual cancer, and repeat ESD was performed at the same location. During the second ESD, pLMs were confirmed yet again in the pathology report, and surgical resection was recommended. However, the patient refused surgery and was lost to follow-up for more than 3 years. At a subsequent visit, an endoscopic biopsy confirmed the presence of remnant cancer with an increased tumor size. The patient underwent subtotal gastrectomy with Billroth II and D2 lymph node dissection. The postoperative pathology confirmed a poorly differentiated adenosquamous carcinoma, with metastasis in 11 of 49 lymph nodes. The final diagnosis was confirmed to be

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Table 1. Comparison of clinicopathological characteristics among patients with positive lateral margins undergoing different additional treatments

Variables	Total (n=123)	Observation (n=108)	Operation (n=13)	Endoscopic treatment (n=2)	P-value*
Age	65±10 (67)	65±10 (67)	63±11 (65)	64±11 (64)	0.688
Sex					0.730
Male	95 (77.2)	82 (75.7)	11 (85.7)	2 (100.0)	
Female	28 (22.8)	26 (24.3)	2 (14.3)		
Tumor location					0.173
Upper third	14 (11.4)	14 (13.1)			
Middle third	50 (40.7)	37 (34.6)	12 (85.7)	1 (50.0)	
Lower third	57 (46.3)	55 (50.5)	1 (14.3)	1 (50.0)	
Remnant stomach	2 (1.6)	2 (1.9)			
Tumor size (cm)	2.8±1.6 (2.8)	2.7±1.6 (2.4)	3.5±1.5 (3.2)	2.7±0.1 (2.7)	0.118
Tumor histology					0.115
WD	58 (47.2)	55 (50.5)	2 (21.4)	1 (50.0)	
MD	45 (36.6)	37 (34.6)	7 (50.0)	1 (50.0)	
PD	5 (4.1)	4 (3.7)	1 (7.1)		
PCC/Mixed	15 (12.2)	12 (11.2)	3 (21.4)		
Tumor depth					0.501
Lamina propria	55 (44.7)	47 (43.0)	7 (57.1)	1 (50.0)	
Muscularis mucosa	59 (48.0)	54 (50.5)	4 (28.6)	1 (50.0)	
Submucosa (sm1)	9 (7.3)	7 (6.5)	2 (14.3)		
Margin involvement multiplicity					0.319
1	86 (69.4)	78 (72.2)	7 (52.0)	1 (50.0)	
2	27 (21.8)	23 (20.4)	3 (28.6)	1 (50.0)	
3	9 (7.3)	8 (7.4)	1 (7.1)		
4	2 (1.6)		2 (14.3)		
Margin length (mm)†	7.0±12.5 (2.0)	4.4±2.0 (7.7)	20.4±12.0 (22.0)	6.5±1.5 (6.5)	0.000
Lauren classification					0.519
Intestinal	101 (82.8)	90 (83.2)	9 (71.4)	2 (100.0)	
Diffuse	12 (9.8)	9 (8.4)	3 (21.4)		
Mixed	9 (7.4)	8 (7.5)	1 (7.1)		
Others		1 (0.9)			
H. pylori infection‡					0.594
Positive	49 (50.5)	43 (50.0)	6 (58.3)		
Negative	48 (49.5)	42 (50.0)	5 (41.7)	1 (100.0)	
Time to additional treatment (day)	425±760 (84)	-	331±816 (84)	384±394 (67)	0.890

Values are presented as mean ± standard deviation (median) or number (%).
WD = well-differentiated tubular adenocarcinoma; MD = moderately differentiated tubular adenocarcinoma; PD = poorly differentiated tubular adenocarcinoma; PCC = poorly cohesive carcinoma; *H. pylori* = *Helicobacter pylori*.
*As the distributions of the three groups did not satisfy normality, a non-parametric method, the Kruskal-Wallis test, was used. The P-value indicates an asymptotic value.
†Only 104 cases for which data were available were analyzed.
‡Only the 97 cases for which data were available were analyzed.

$pT_3N_{3a}M_0$ Stage III_b. The patient received eight cycles of XELOX as adjuvant chemotherapy. Following the chemotherapy, no recurrence has been observed.

Long-term follow-up outcomes

The long-term prognosis of all patients is demonstrated in **Fig. 1**. In the observation group, 28 patients with remnant cancer were identified during the follow-up, and 12 (42.9%) underwent further surgical treatment. Two of the 12 patients (16.7%) were lost to follow-up. Of the remaining 10 patients, one had confirmed extra-gastric lymph node metastases (**Table 3**). None of the 10 patients experienced further recurrence. Of the 28 patients, 15 (53.6%) were treated endoscopically, four (26.7%) underwent additional ESD, and 11 (73.3%) underwent APC cauterization. None of the 15 patients experienced any further recurrence. One of the 28 patients was lost to follow-up without further treatment, as per the patient's preference.

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Table 2. Comparison of clinicopathological characteristics of observation group with pLMs and 1:1 matched curative resection group

Variables	Curative resection group (n=108)	Observation group with pLMs (n=108)		P-value*
		Remnant tumor (n=28)	No Remnant tumor (n=80)	
Age	65±9.8 (66)	65±10 (67)	66±10 (67)	0.810 (0.655)
Sex				0.221 (0.249)
Male	76 (70.1)	19 (66.7)	63 (78.8)	
Female	32 (29.9)	9 (33.3)	17 (21.3)	
Tumor location				0.733 (0.582)
Upper third	14 (13.1)	1 (3.7)	13 (16.3)	
Middle third	45 (42.1)	12 (44.4)	26 (32.5)	
Lower third	48 (43.9)	15 (51.9)	39 (48.8)	
Remnant stomach	1 (0.9)		2 (2.5)	
Tumor size (cm)	3.8±0.8 (3.6)	2.9±1.4 (3.0)	2.7±1.6 (2.0)	0.000 (0.540)
Tumor histology				0.376 (0.158)
WD	48 (43.9)	12 (38.5)	44 (54.3)	
MD	49 (45.8)	9 (34.6)	28 (34.6)	
PD	3 (2.8)	4 (15.4)		
PCC/Mixed	8 (7.5)	3 (11.5)	9 (11.1)	
Tumor depth				0.064 (0.854)
Lamina propria	33 (29.9)	13 (44.4)	34 (42.5)	
Muscularis mucosa	59 (55.1)	13 (48.1)	41 (51.3)	
Submucosa (sm1)	16 (15.0)	2 (7.4)	5 (6.3)	
Margin involvement multiplicity†				N/A (0.331)
1		22 (81.5)	55 (68.8)	
2		5 (14.8)	18 (22.5)	
3		1 (3.7)	7 (8.8)	
Margin length (mm)†‡		5.2±7.6 (2.0)	4.2±7.6 (2.0)	N/A (0.592)
Lauren classification				0.721 (0.394)
Intestinal	93 (86.0)	16 (55.6)	74 (92.5)	
Diffuse	9 (8.4)	7 (25.9)	2 (2.5)	
Mixed	6 (5.6)	4 (14.8)	4 (5.0)	
Others		1 (3.7)		
H. pylori infection§				0.071 (0.493)
Positive	30 (36.3)	12 (57.9)	31 (47.7)	
Negative	51 (63.8)	8 (42.1)	34 (52.3)	

Values are presented as mean ± standard deviation (median) or number (%).
pLMs = positive lateral margins; WD = well-differentiated tubular adenocarcinoma; MD = moderately differentiated tubular adenocarcinoma; PD = poorly differentiated tubular adenocarcinoma; PCC = poorly cohesive carcinoma; *H. pylori* = *Helicobacter pylori*.
*Curative resection group compared to the observation group. P-values in parentheses indicate comparisons between subgroups with and without remnant tumors within the observation group.
†Not applicable to curative resection group.
‡Only the 86 cases for which data were available were analyzed. Only 81 cases in the curative group and 84 cases in the observation group for which data were available were analyzed.

Table 3. Clinical features of patients who had extra-gastric metastasis (n=1)

Type of recurrences	Age/ Sex	Location	Size (cm)	Initial ESD Pathology (Op pathology)	Depth	Lauren	Involved margin number	Involved margin length (mm)	Ulcer	*H. pylori* infection	Surgery	Lymphatic/ Venous invasion	Metastatic LN location	Specific consideration
Extra-gastric metastasis	61/M	Lower third	2.8	MD (PD)	Muscularis mucosa	Intestinal	2 (Distal, anterior)	34	(–)	(+)	STG B-II (D2 LN dissection)	+/+	11 of 49	Initially Op was recommended but the patient refused, however, 3 years later Op was performed. Treatment after Op: adj. XELOX #8.

ESD = endoscopic submucosal dissection; Op = operation; *H. pylori* = *Helicobacter pylori*; LN = lymph node; MD = moderately differentiated tubular adenocarcinoma; PD = poorly differentiated tubular adenocarcinoma; STG = subtotal gastrectomy; B-II = Billroth II ; adj. = adjuvant.

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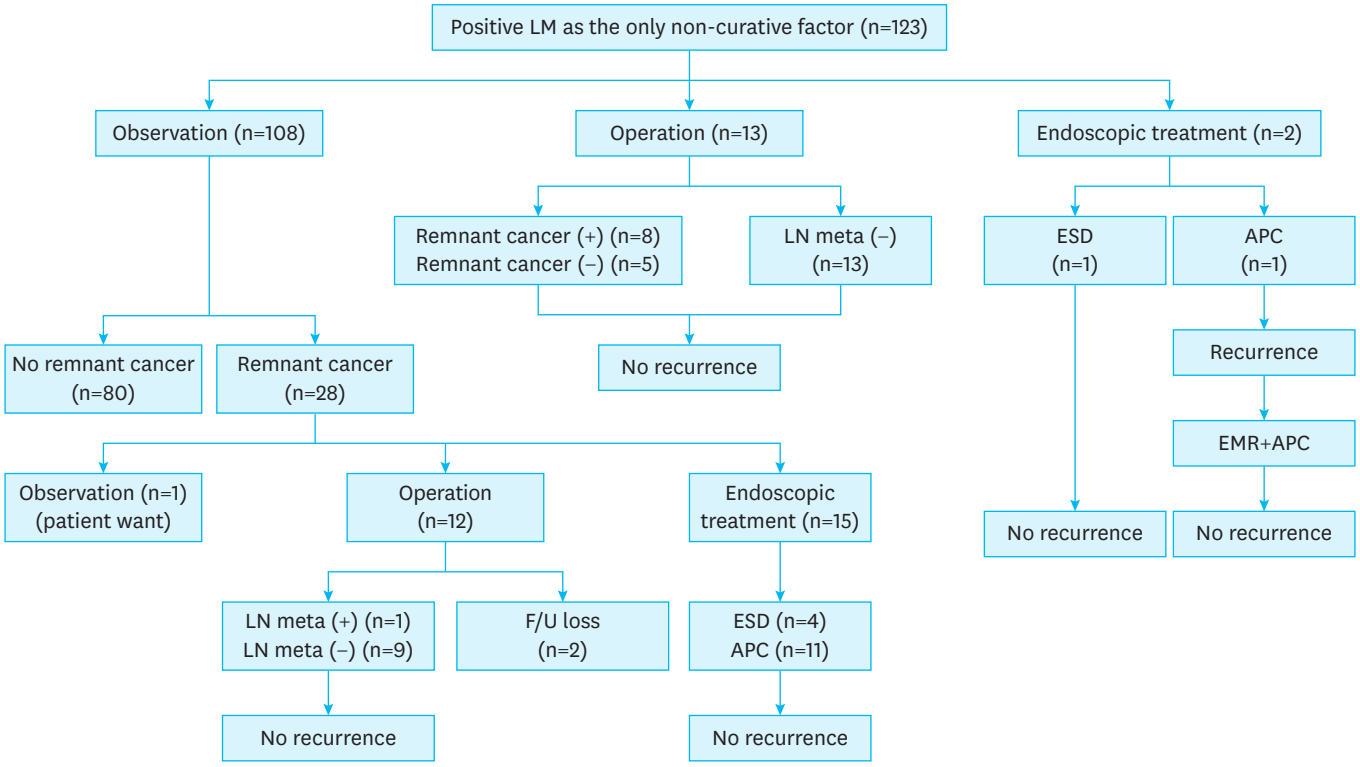

Fig. 1. Long-term outcomes of cases with positive lateral margins as the only non-curative factor.
LM = lateral margin; LN = lymph node; ESD = endoscopic submucosal dissection; APC = argon plasma coagulation; EMR = endoscopic mucosal resection.

Thirteen patients had pLMs identified on the initial ESD and underwent immediate surgical treatment. Eight patients (61.5%) had remnant cancer identified in their postoperative specimens, and five patients (38.5%) had no remnant cancer identified. None of the 13 patients had extra-gastric lymph node metastases, and there were no further recurrences at follow-up.

Two patients had pLMs identified on the initial ESD and underwent immediate endoscopic treatment. One patient (50.0%) underwent additional curative ESD and has remained recurrence-free since then. The other patient (50.0%) underwent APC cautery and was recurrence during follow-up. In this case, the area around the lesion was marked with APC, a saline injection was performed, the lesion was removed by endoscopic mucosal resection (EMR) using a snare, and the remaining lesion was coagulated with APC. No recurrences were observed.

Comparison of the observation group and the curative group

Approximately, 28 (25.9%) recurrences were identified in the observation group after pLMs were detected. Zero (0.0%) recurrences were observed in the curative resection group and 1:1 matched cured group through propensity score matching. When analyzing the difference in recurrence rates between the two groups using McNemar's test, the recurrence rate was discovered to be statistically significant (P=0.00) in the observation group. However, when comparing the survival of the two groups using Kaplan–Meier survival curves for overall survival, the log-rank test exhibited no difference in survival between the two groups (P=0.577) (**Fig. 2**).

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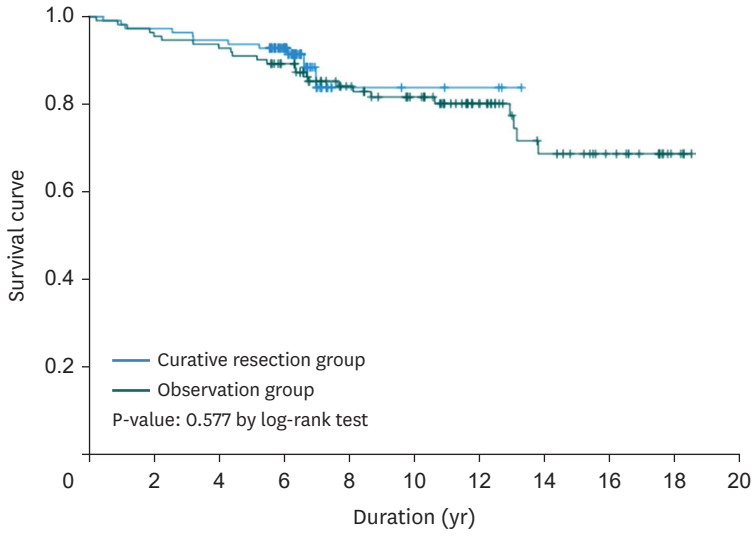

Fig. 2. Survival curve of matched positive lateral margins groups and curative group.

DISCUSSION

With the development of endoscopic techniques, ESD has been widely performed for EGCs [12,13]; therefore, establishing a subsequent treatment when non-curative ESD is performed is important [14]. Retrospective studies have demonstrated that the risk of lymph node metastasis is negligible when the reason for non-curative resection is invasion of the lateral or deep margins [3,15]. However, subsequent treatment is not clearly defined when pLMs are identified as the only non-curative factor. Studies of the presence of pLMs alone after ESD are rare, and the long-term prognosis of these patients is unknown [16,17].

This study tracked the long-term outcomes of patients who underwent non-curative ESD and whose pLMs were the only non-curative factors. Patients were categorized into observation, immediate surgery, and immediate endoscopic treatment groups. For the most part, no statistical differences were identified between the three groups, but the immediate surgery group had a significantly longer invaded lateral margin length than that in the other groups. According to the clinician, the immediate surgery group was likely to have a high risk of recurrence. This is consistent with previous findings demonstrating that a long lateral margin is associated with a high risk of recurrence [18]. No statistically significant differences were observed among the other factors.

Regarding positive tumor margin length, a previous study suggested a cutoff value of 6 mm to predict remnant cancer [18]; however, in our study, no statistical difference was present between the observation groups for remnant tumors (n=28, 5.2 mm) and the group with no remnant tumors (n=108, 4.2 mm). This could be explained by the fact that immediate surgery was previously performed in cases with long tumor margins (n=13, 20.4 mm).

No postoperative recurrence was observed in the immediate surgery group. In the immediate endoscopic group, one patient was treated with APC to cauterize the remnant tumor; however, recurrence was confirmed and subsequently re-treated with a combination of EMR and APC. In this case, the patient was old and had many comorbidities; therefore, APC was selected as the primary treatment, which may have resulted in an insufficient remnant tumor [19]. No additional recurrence was identified after retreatment with EMR or APC.

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This study analyzed the outcomes and prognosis of patients who underwent incomplete ESD and were closely followed up. For comparison, a propensity score was calculated and used to match patients in a 1:1 ratio between the group that underwent curative resection and the group that was followed up after pLMs confirmation. Compared with the curative resection group, the observation group had a significantly higher recurrence rate, which is consistent with the findings of the previous studies demonstrating that pLMs are a risk factor for remnant tumors [20]. In cases where recurrence was identified during surveillance, surgery or endoscopic treatment was performed, and surveillance of the patient's volition was continued in only one case. No recurrence was observed after surgery or endoscopic treatment. Only one case of extra-gastric metastasis was identified during follow-up. The case involved a patient who was originally recommended for immediate surgery, but the patient voluntarily refused treatment and the time for appropriate treatment had passed. After the patient underwent surgery and subsequent adjuvant chemotherapy, no additional recurrence was observed.

Few previous studies have demonstrated long-term survival after incomplete ESD, with an average of 5.0 years [18] and 5.1 years [21]. Our study demonstrated a prolonged follow-up duration with a median duration of 8.2 and presented long-term clinical outcomes in the group with curative resection. Two possible explanations exist for the lack of a difference in survival between the pLMs group and curative resection groups, despite the presence of pLMs. First, cases with pLMs were overestimated. Endoscopically resected tissue is usually immediately fixed in formalin; however, the elasticity of the tissue itself does not completely prevent the curling of the edges. In these cases, a narrow margin of safety can cause the edges to curl and resemble pLMs, even if the margin is negative. Patients with false-positive pLMs underwent curative resection. Second, when ESD is performed after the lesion is removed, the margins of what remains are usually cauterized during the pre-cutting phase or hemostasis. Even if a minimal remnant tumor exists on the border, the remnant tumor can be spontaneously electro-ablated. However, in the case of long-margin-positive tumors, this effect is less likely to occur.

The choice of follow-up treatment after incomplete ESD remains challenging. At the hospital, we followed the three-step approach described above. When deciding on subsequent treatment, oncological R2 resection is immediately followed by endoscopic or surgical treatment. If the cancer was pathologically aggressive, immediate intervention was initiated. This policy is strongly supported by the fact that only a single patient in the study with confirmed extra-gastric metastasis underwent oncologic R2 resection; however, the patient refused to undergo additional surgery. If a patient was identified to have undergone oncologic R1 resection, decisions regarding the subsequent course of treatment also factored in comorbidities and age. The overriding consideration is to avoid recurrence; however, given that surgical intervention may impact the quality of life post-surgery, additional endoscopic treatment involves a decrease in the effectiveness of the procedure if it is performed in the same location where the ESD was performed, alongside challenges posed by numerous comorbidities in patients; careful observation is an acceptable follow-up option. In our study, residual cancer was detected in 25% of the patients in the observation group, but none of the patients who had received regular surveillance had extra-gastric metastasis. Furthermore, no additional cancer recurrence was observed after the additional treatment. As the guidelines are not established, personalizing the treatment for each patient is important.

This study has several limitations. First, observations without immediate treatment after incomplete ESD may raise ethical concerns. However, in the present study, we selected a follow-up treatment policy in accordance with our guidelines to avoid extra-gastric

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recurrence. In our study, no deaths were reported due to recurrence or extra-gastric metastasis among patients under regular surveillance. Second, this was a retrospective study conducted at a single center, which may have resulted in selection bias, and the limited number of cases for each treatment modality warrants further large studies. Third, the retrospective study design did not allow us to adjust for operator reliance on the treatment selection or procedural skills. However, we limited the number of experienced endoscopists who performed ESD. Finally, the follow-up period was long and included individuals who underwent ESD up to 20 years ago. Consequently, variability in the expertise of pathology readers and inconsistency in the format of result sheets may have introduced confounding variables into the study results.

In conclusion, when pLMs are the only non-curative factor, the long-term prognosis with appropriate treatment or close observation appears to be comparable to that with curative resection. Therefore, watchful waiting can be included as an option if close and regular follow-up is feasible at the discretion of the clinician.

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