Original Article

The effects of oral steroid duration on stricture prevention after extensive endoscopic submucosal dissection for superficial esophageal cancer

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Background: Esophageal stricture is a major complication of endoscopic submucosal dissection (ESD) in patients with superficial esophageal cancer (SEC). Oral steroids have been used to prevent esophageal stricture in patients with more than 75% of the esophageal circumference resected. However, there are no established guidelines regarding the optimal duration of steroid use. This retrospective observational study aimed to compare the incidence of esophageal stricture according to the period of prophylactic oral steroid use and to identify the risk factors for esophageal stricture.

Methods: Eighty-one patients who were prescribed prophylactic steroid after undergoing ESD for SEC with more than 75% of esophageal circumference resected were enrolled. Patients were classified into the four-week steroid group (n=72) or eight-week steroid group (n=9) to compare the incidence of esophageal stricture. In addition, the patients were subdivided into those who developed esophageal stricture (n=24) and those who did not (n=57) to identify the risk factors for esophageal stricture.

Results: Twenty patients (27.8%) in the four-week oral steroid group and four patients (44.4%) in the eight-week oral steroid group developed esophageal stricture (P=0.44). The univariable analysis identified tumor size, longitudinal length of semi-circumferential resection, and proportion of circumferential resection as risk factors of esophageal stricture. The multivariable analysis identified the proportion of circumferential resection as an independent risk factor. After adjusting for the proportion of circumferential resection, the incidence of stricture was marginally higher in the eight-week steroid group [P=0.05; odds ratio (OR): 5.69; 95% confidence interval (CI): 1.01–32.15].

Conclusions: Eight weeks of oral steroid prophylaxis does not reduce the risk of stricture after extensive ESD more than four weeks of oral steroid prophylaxis. The proportion of circumferential resection is the strongest risk factor for stricture in patients with SEC undergoing ESD.

Keywords: Superficial esophageal cancer (SEC); esophageal stricture; endoscopic submucosal dissection (ESD); oral steroid prophylaxis; circumferential resection of esophagus

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Introduction

Endoscopic submucosal dissection (ESD) is a minimally-invasive procedure that improves the quality of life for patients with superficial esophageal cancer (SEC) by promoting early recovery and requiring a short hospital stay (1,2). However, the procedure results in esophageal stricture in 6.5–16.7% of patients (3,4). The incidence of esophageal stricture increases to 45–92% if more than 75% of the esophageal circumference is resected; therefore, various methods have been studied to prevent stricture (2,5-7), including prophylactic oral steroid therapy. Prophylactic oral steroid therapy has been proven to be effective and is currently used for the prevention of esophageal stricture in patients who undergo resection of more than 75% of the esophagus circumference (8,9). Prophylactic oral steroids are typically administered for eight weeks, including two weeks of 0.5–1 mg/kg/day followed by a six-week taper, in accordance with many Japanese studies (8-12). However, the prolonged use of steroids elevates the risk of adverse effects (7-9). A recent study reported that a shorter oral steroid regimen lasting three weeks is also effective for the prevention of esophageal stricture (9,13). As most cases of stricture occur within two weeks of the procedure, the use of a four-week steroid prophylaxis regimen is gradually increasing in clinical practice. However, there are no established guidelines regarding the duration of steroid therapy, and relevant large-scale studies are lacking. Further, studies regarding the risk factors of esophageal stricture are limited to those focused on ≥75% esophageal circumferential resection (3).

This study aimed to compare the incidence of esophageal stricture according to the duration of steroid therapy in patients who underwent ESD to resect more than 75% of the esophageal circumference after being diagnosed with SEC. The study also aimed to identify the risk factors of esophageal stricture other than the area of circumferential resection. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1990/rc).

Methods

Patients

The data of 545 patients who underwent ESD for SEC between January 2015 and May 2020 were retrospectively reviewed. Eighty-one of these patients had more than 75% of the esophageal circumference resected and were prescribed prophylactic steroid therapy; thus, this study included 81 patients. Patients with incomplete ESD, a follow-up period of less than four weeks, a history of esophageal chemotherapy or radiation therapy, suspected lesions beyond the submucosal layer, two or more lesions, or hemorrhage or perforations after ESD were excluded from this study. Patients who received steroids due to another disease were also excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of the Samsung Medical Center on October 26, 2020 (No. 2020-09-036-001). The review board waived the requirement of informed consent, because this study was not risky for the patients.

ESD procedure

ESD was performed under general anesthesia using a forward-viewing endoscope (GIF Q260J; Olympus, Tokyo, Japan) and an electrosurgical unit (ERBE Elektronedizin, Tübingen, Germany). The tumor margins were identified using a lugol solution, and the outer circumference of the tumor margin was dotted using a dual knife (KD-650; Olympus Medical Systems, Tokyo, Japan). Then, a submucosal injection was performed using a mixture of normal saline, 0.005% epinephrine, and indigo carmine, and a circumferential incision and submucosal dissection were performed using a dual knife. Bleeding during and after the procedure was controlled with hemostatic forceps (FD410LR; Olympus), and the resected specimens were collected using endoscopic suction.

Steroid administration

Overall, seventy-two patients received oral prednisolone for four weeks and nine received oral prednisolone for eight weeks. The four-week steroid group was administered 30 mg of oral steroids three days after ESD, which was gradually tapered over four weeks (daily dose: 30, 30, 20, and 10 mg for seven days each). The eight-week steroid group was administered 30 mg of oral steroid three days after ESD, which was gradually tapered over eight weeks (daily dose: 30, 30, 25, 25, 20, 15, 10, and 5 mg for seven days each). Prophylactic oral steroids were used for patients who underwent ESD with resection of more than 75% of the esophageal circumference for SEC. From 2015 to 2016, four- or eight-week regimens were used according to the operator's assessment of the morphological characteristics of the lesion. Beginning in 2017, oral steroids were administered for four weeks regardless of the characteristics of the lesion. This study retrospectively compared the data of patients who received eight weeks of oral steroid therapy between 2015 and 2016 to that of patients who received four weeks of oral steroid therapy after 2017.

Definitions

Several studies have reported that resecting more than 75% of the esophageal circumference significantly increases the risk of esophageal stricture (8,14-16). In this study, the following parameters were examined to determine whether other factors affect esophageal stricture: tumor size, depth of invasion, longitudinal length of semi-circumferential resection (LOCR), and proportion of semi-circumferential resection (POCR).

The tumor size was analyzed as a continuous variable based on the length of the specimen. The LOCR refers to the longitudinal length of the esophageal area resected by more than 75% during ESD and was analyzed as a continuous variable. The POCR was categorized as 6/8–7/8 (75–87.5%), 7/8–8/8 (87.5–100%), or 8/8 (100%) based on the proportion of the resection that included more than 75% of the esophagus circumference. The depth of invasion was classified as mucosal invasion or submucosal invasion, defined as tumor invasion beyond the muscularis mucosa. Three highly experienced gastroenterologists (YW Min, DK Lee, and JY Kim) reviewed the endoscopic images to evaluate the LOCR and POCR.

Follow up and study objectives

The presence of stricture was determined via a conventional endoscope when the patient complained of dysphagia following ESD, and endoscopic balloon dilatation was performed if the stricture was confirmed. Patients without dysphagia underwent routine surveillance endoscopy eight weeks after the procedure. Stricture was defined as difficulty swallowing solid foods or difficulty passing a conventional endoscope with an outer diameter less than 10 mm. The primary objective was to compare the incidence of stricture between the four-week and eight-week oral steroid groups after ESD. The secondary objective was to identify the risk factors of stricture by comparing patients who developed a stricture after ESD with those who did not.

Statistical analysis

Descriptive data are presented as mean ± standard deviation or median and interquartile range (IQR), and categorical data are presented as number and percentage or frequency (1). The Student *t*-test, Wilcoxon rank sum test, and Fisher's exact test were used to compare the groups, as appropriate. Multivariable and univariable analyses of the risk factors for esophageal stricture were performed using logistic regression analysis. Statistical significance was set at $P<0.05$. All statistical analyses were conducted using SPSS version 25.0 (IBM, NY, USA)

Results

Baseline characteristics

Eighty-one patients who had more than 75% of their esophageal circumference resected via ESD were divided into the four-week steroid group (n=72) and eight-week steroid group (n=9). The number of patients with stricture that was determined via difficulty passing a conventional 10 mm diameter endoscope were 15 out of 81 (19%) and that confirmed by difficulty in swallowing was and 66 (81%). *Table 1* shows the baseline clinicopathological characteristics. There were no significant differences in age (P=0.32), body mass index (BMI) (P=0.41), sex (P=0.52), smoking (P=0.62), diabetes mellitus (P>0.99), tumor size (P=0.44), LOCR (P=0.06), POCR (P=0.28), tumor location (P=0.85), or depth of tumor invasion (P=0.72) between the two groups (*Table 1*).

Table 1 Patient clinicopathological characteristics

Variables	Oral steroid 4-week (n=72)	Oral steroid 8-week (n=9)	P value
Age	67.5±8.1	64.7±7.1	0.32
BMI	23.7±2.9	24.5±1.7	0.41
Sex, n (%)			
Male	67 (93.1)	8 (88.9)	0.52
Smoking, n (%)			0.62
Current smoker	9 (12.5)	2 (22.2)	
Ex-smoker	41 (56.9)	4 (44.4)	
Never smoked	22 (30.6)	3 (33.3)	
DM, n (%)			
Yes	20 (27.8)	2 (22.2)	> 0.99
Tumor size (cm)	3.4 (2.6–4.3)	3.1 (3–3.2)	0.44
LOCR (cm)	3.0 (2.0–4.0)	2 (1.5–2.5)	0.06
POCR, n (%)			0.28
75.0–87.5%	26 (36.1)	6 (66.7)	
87.5–100%	27 (37.5)	2 (22.2)	
100%	19 (26.4)	1 (11.1)	
Tumor location, n (%)			0.85
Upper thoracic	5 (6.9)	0 (0)	
Middle thoracic	29 (40.3)	3 (33.3)	
Lower thoracic	38 (52.8)	6 (66.7)	
Depth of tumor invasion, n (%)			0.72
Mucosal layer	50 (69.4)	7 (77.8)	
SM layer	22 (30.6)	2 (22.2)	
Stricture, n (%)			
No	52 (72.2)	5 (55.5)	0.44
Yes	20 (27.8)	4 (44.4)	

Data are presented as mean standard deviation or number (frequency). BMI, body mass index; DM, diabetes mellitus; SM, submucosal layer; LOCR, longitudinal length of semi or total circumferential resection; POCR, proportion of semi-circumferential resection.

Stricture rate

Esophageal stricture occurred in 20/72 patients (27.8%) in the four-week steroid group and in 4/9 patients in the eight-week steroid group (44.4%) (P=0.44) (*Table 1*).

Risk factors for stricture

The patients were divided into those who did not develop stricture (n=57) and those who did develop stricture (n=24). Tumor size was identified as a significant predictor of stricture, with a significantly larger tumor size in the stricture group [odds ratio (OR): 1.54; 95% confidence interval (CI): 1.00–2.36; P=0.05]. The LOCR was also significantly larger in the stricture group (OR: 1.49: 95% CI: 1.07–2.09; P=0.02). A POCR of 7/8–8/8 (87.5–100%) was associated with a higher incidence of stricture compared to the 6/8–7/8 (75–87.5%) group, though the difference

Table 2 Risk factors for post-ESD esophageal stricture

Variables	No stricture (n=57)	Stricture (n=24)	Univariable model	
			OR (95% CI)	P value
Age	67.3±8.1	67.1±8.0	1.00 (0.94–1.06)	0.93
BMI	23.8±2.9	23.7±2.6	0.99 (0.83–1.18)	0.91
Sex, n (%)				
Male	52 (69.3)	23 (30.7)	1 (ref)	
Female	5 (83.3)	1 (16.7)	0.45 (0.05–4.09)	0.48
Smoking, n (%)				
Current smoker	9 (81.8)	2 (18.2)	1 (ref)	
Ex-smoker	32 (71.1)	13 (28.9)	1.83 (0.35–9.64)	0.80
Never smoked	16 (64.0)	9 (36.0)	2.53 (0.45–14.37)	0.29
DM, n (%)				
No	43 (72.9)	16 (27.1)	1 (ref)	
Yes	14 (63.6)	8 (36.4)	1.54 (0.54–4.35)	0.42
Tumor size (cm)	3.1±1.0	3.7±1.6	1.54 (1.00–2.36)	0.05
LOCR (cm)	2.5 (2.0–4.0)	3.5 (2.8–4.8)	1.49 (1.07–2.09)	0.02
POCR, n (%)				
75.0–87.5%	28 (87.5)	4 (12.5)	1 (ref)	
87.5–100%	23 (79.3)	6 (20.7)	1.83 (0.46–7.26)	0.17
100%	6 (30.0)	14 (70.0)	16.33 (3.95–67.45)	<0.001
Tumor location, n (%)				
Upper thoracic	2 (40.0)	3 (60.0)	1 (ref)	
Middle thoracic	23 (71.9)	9 (28.1)	0.26 (0.04–1.83)	0.30
Lower thoracic	32 (72.7)	12 (27.3)	0.25 (0.04–1.69)	0.24
Depth of tumor invasion, n (%)				
Mucosal layer	38 (66.7)	19 (33.3)	1 (ref)	
SM layer	19 (79.2)	5 (20.8)	0.53 (0.17–1.63)	0.27

Data are presented as mean ± standard deviation, median (interquartile range), or number (frequency). ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; SM, submucosal layer; LOCR, longitudinal length of semi-circumferential resection; POCR, proportion of semi-circumferential resection.

was not significant (OR: 1.83; 95% CI: 0.46–7.26; P=0.17). A POCR of 8/8 (100%) was associated with a higher incidence of stricture compared to the 6/8–7/8 (75–87.5%) (OR: 16.33; 95% CI: 3.95–67.45; P<0.001) (*Table 2*).

A POCR of 8/8 (100%) was identified as an independent risk factor for stricture compared to 6/8–7/8 (75–87.5%) (OR: 25.90; 95% CI: 5.17–129.77; P<0.001). The incidence of stricture was compared between the four-week and eight-week steroid groups after adjusting for this variable, and the incidence of stricture was not significantly different between the two groups (*Table 3*).

Discussion

Eight weeks of prophylactic oral steroids did not result in a significant decrease in the rate of esophageal stricture

Table 3 Independent risk factors for post-endoscopic submucosal dissection esophageal stricture

Variables	No stricture (n=57)	Stricture (n=24)	Multivariable model	
			OR (95% CI)	P value
Tumor size (cm)	3.1±1.0	3.7±1.6	1.19 (0.72–1.95)	0.48
LOCR (cm)	2.5 (2.0–4.0)	3.5 (2.8–4.8)	0.95 (0.61–1.52)	0.83
POCR, n (%)				
75.0–87.5%	28 (87.5)	4 (12.5)	1 (ref)	
87.5–100%	23 (79.3)	6 (20.7)	2.59 (0.56–11.94)	0.22
100%	6 (30.0)	14 (70.0)	25.90 (5.17–129.77)	<0.001
Oral steroid, n (%)				
4-week regimen	52 (72.2)	20 (27.8)	1 (ref)	
8-week regimen	5 (55.6)	4 (44.4)	5.69 (1.01–32.15)	0.05

Data are presented as mean ± standard deviation, median (interquartile range), or number (frequency). OR, odds ratio; CI, confidence interval; LOCR, longitudinal length of semi-circumferential resection; POCR, proportion of semi-circumferential resection.

compared to four weeks of prophylactic oral steroids in this study. Esophageal ESD is a minimally invasive procedure associated with early recovery, a short hospital stay, improvement in the quality of life, and low complications in patients with SEC (1). However, esophageal stricture is a major complication of ESD that leads to dysphagia and aspiration pneumonia, ultimately affecting the patient's quality of life (2,17). The incidence of post-ESD esophageal stricture is reported as 6.5–16.7%, with an incidence of 45.5–92% if more than 75% of the esophageal circumference is resected (4,5). Several methods have been used to prevent esophageal stricture. Oral steroids are known to be effective to prevent esophageal stricture, but few studies have standardized the regimens for the administration of prophylactic oral steroids after ESD for SEC.

Yamaguchi *et al.* (8) reported that the prophylactic use of steroids helps prevent esophageal stricture in a study comparing the incidence of esophageal stricture in patients who underwent prophylactic endoscopic balloon dilation and those who underwent eight weeks of prophylactic oral steroid therapy after complete circumferential or semi-circumferential ESD due to SEC. The incidence of stricture and the number of endoscopic balloon dilatations performed due to stricture were significantly lower in the oral steroid group, suggesting the efficacy of oral steroids.

Recently, intra-lesional steroid injections have been proposed as a method to prevent esophageal stricture while reducing the general adverse effects of oral steroids. Hashimoto *et al.* (18) reported that post-ESD prophylactic steroid injections help prevent esophageal stricture, as the rate of esophageal stricture was 19% among patients who received a triamcinolone injection after semicircular ESD for SEC, which was significantly lower than that in the control group (75%). In 2019, Pih *et al.* (1) reported that 20% of patients with SEC who received oral steroids after an ESD involving more than 75% of the esophagus circumference experienced esophageal stricture, compared to 33.3% of patients who received steroid injections and 50% of the control group. Morikawa *et al.* (19) reported a patient with esophageal stricture that was refractory to intra-lesional steroid injections but responded to systemic steroid treatments, suggesting that systemic steroids are a more effective treatment for fibrotic tissues. Other methods to prevent esophageal stricture include the transplantation of autologous cell sheets and polyglycolic acid (PGA) sheet deployment with fibrin glue; however, there are few studies regarding these methods, and oral steroids are the most widely-used method to prevent esophageal stricture after esophageal ESD. However, the dosage and administration of oral steroids to prevent esophageal stricture after ESD for SEC have not been standardized.

Most previous studies that have investigated the use of oral steroids for the prevention of esophageal stricture used an eight-week regimen with a starting prednisolone dose 30 mg that is then tapered, resulting in a significant reduction of the stricture rate (8,10,11). A prednisolone dose of 30 mg/day is a moderate dose that is generally

used for inflammatory bowel disease and collagen-related disorders and has been proven to be effective with few severe adverse effects if used short-term (15,20). However, the total dose of prednisolone administered during the eight-week regimen exceeds 1,000 mg; therefore, the possibility of prednisolone-related adverse events must be taken into consideration. Although there were no reports of prednisolone-related adverse events in this study, as the risk of peptic ulcers, osteoporosis, diabetes, optical damage, psychiatric disturbances, pneumocystis pneumonia, and esophageal candidiasis are elevated when an eight-week oral steroid regimen is used (8,9,20). Therefore, it is clinically important to determine if this extended steroid regimen provides any clinical benefits compared to the four-week regimen.

In 2015, Kataoka *et al.* (13) reported that the incidence of stricture is significantly lower in patients receiving a three-week regimen of prednisolone group compared to those who did not receive prophylactic oral steroids after semi- or total circumference esophageal resection. Although this previous study included few patients (n=33), the results indicated that low-dose oral steroids are effective to prevent esophageal stricture.

This study aimed to identify the optimal duration of oral steroids for the effective prevention of esophageal stricture and to identify the risk factors for esophageal stricture. In this study, 24/81 (29.6%) patients who were administered prophylactic steroids after undergoing an esophageal resection of more than 75% of their esophageal circumference due to SEC developed an esophageal stricture. Esophageal strictures occurred in 20/72 patients (27.8%) in the four-week steroid group and 4/9 patients (44.4%) in the eight-week steroid group, which was not significantly different. Tumor size, the LOCR, and the POCR were identified as predictors of esophageal stricture, and the POCR was found to be an independent predictor of esophageal stricture. The incidence of stricture was significantly higher in patients who underwent a total circumferential resection compared to those who underwent a semi-circumferential resection. These results indicate that semi-circumferential resection is preferred when determining the range of resection during ESD if the lesion margins are secured. The LOCR and tumor size significantly affected the incidence of stricture in the univariable analysis (P=0.02 and P=0.05, respectively). The incidence of stricture was higher when the LOCR was longer and the tumor size was larger. However in the multivariable analysis, these risk factor did not identified as independent risk factors of stricture. This may have been due to the small sample size included in this study. Hence, these variables should be re-examined in future, large-scale studies.

When the incidence of stricture was compared between the four- and eight-week steroid groups after adjusting for the POCR, the incidence of stricture was slightly higher in the eight-week steroid group than in the four-week group (OR: 5.69; 95% CI: 1.01–32.15; P=0.05), suggesting that the development of esophageal strictures is influenced more by the characteristics of the resected specimen than the duration of steroid use. Although this bias was removed when comparing the effects of the duration of steroid treatment, confounding factors remained and may have increased the relative risk of esophageal stricture. Therefore, further prospective randomized trials are necessary to confirm the results of this study.

Esophageal stricture is known to occur as the esophageal mucosal defect heals after ESD (21). This healing process can be summarized into three stages: inflammatory response, epithelial proliferation, and extracellular matrix remodeling (22). A histological examination of the healing of esophageal mucosal defects in animals that underwent esophageal mucosal resection showed ulcer formation and inflammatory cell invasion on postoperative days (PODs) 2–4, angiogenesis and hyperplasia of collagen fiber on POD 7, and fibrosis on POD 28 (23). Based on these results, it is believed that postoperative esophageal stricture occurs as a result of reduced elasticity and movement of the esophageal wall due to fibrosis in the submucosal and proper muscle layers during mucosal defect healing (6,23). Therefore, it is important to inhibit inflammatory responses and collagen synthesis to prevent stricture.

Corticosteroids can inhibit stricture by inhibiting anti-inflammatory actions and collagen synthesis and promoting collagen degradation (24-26). Honda *et al.* (23) reported that infiltration of inflammatory cells occurs early after postoperative mucosal defects and fibrosis occurs within four weeks. Therefore, it is important to prevent early inflammation and inhibit collagen fiber synthesis via the early administration of systemic steroids. Furthermore, the use of systemic steroids an additional four weeks after fibrosis has already occurred would not significantly contribute to preventing esophageal stricture. This speculation was partially confirmed in this study, as eight weeks of steroid treatment did not reduce the risk of stricture compared to four weeks of treatment.

Given that the duration of steroid administration was

determined according to the operator's assessment in the cases of ESD between 2015 to 2016, potential for selection bias exists. However, after 2017, four-week regimens were used for every case regardless of the lesion characteristics, and the number of cases included in this group was much larger. In addition, we tried to reduce selection bias as much as possible through the process of adjusting factors affecting stricture through multivariate analysis. However, considering that there is still a risk of bias, we think our results need to be interpreted under this background.

This study is not without limitations. First, this was a retrospective, nonrandomized, single-center study with potential selection and referral biases. Second, the sample size was small; in particular, the number of patients in the eight-week steroid group was small compared to that in the four-week steroid group. This may be the reason that some risk factors for stricture identified in previous studies (depth of invasion and tumor size) were not confirmed to be significant in the multivariable analysis in this study (4,16,27). The small sample size may also account for the fact that the incidence of stricture was higher in the eight-week steroid group in the multivariable analysis. A future large-scale randomized trial should be conducted to further evaluate these factors. Third, the LOCR was measured via a review of endoscopic images. Although these measurements were obtained by three skilled endoscopy specialists, mismeasurements cannot be ruled out. Objective measurement techniques should be used in future studies.

Conclusions

In this study, eight weeks of oral steroid prophylaxis may not reduce the risk of stricture after extensive esophageal ESD compared to four weeks of treatment. These results suggest that a four-week oral steroid regimen could be enough for the prevention of significant esophageal stricture following extensive esophageal ESD regarding the adverse effect of the longer duration of steroid use. The POCR is the most potent independent risk factor for post-ESD esophageal stricture in patients who had more than 75% of the esophageal circumference resected in this study. Further large-scale prospective studies are necessary to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1990/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1990/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1990/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the institutional review board of Samsung Medical Center (No. 2020-09-036-001, date: October 26, 2020). Informed consent was waived for this retrospective analysis, because this study was not risky for the patients.

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