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Risk factors of refractory post-endoscopic submucosal dissection esophageal strictures

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ABSTRACT

Introduction: our aim was to comparatively assess the treatment outcomes of endoscopic dilatation in Barrett's neoplasia and squamous cell carcinoma (SCC) post-endoscopic submucosal dissection (ESD) strictures, and to determine the risk or factors associated to refractory strictures.

Methods: an observational study. All consecutive patients presenting with a post-ESD stricture in 2007-2016 who underwent dilation therapy were included. Clinical, morphological, and technical features were assessed to determine the risk factors of

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refractory strictures.

Results: of 414 consecutive patients treated by ESD, 83 (mean age: 65 ± 10 years, 76 % men) with 254 dilations (median: 3, range: 1-27) were considered. Barrett's neoplasia and SCC were the indications in 58 (69.9 %) and in 25 (30.1 %) cases, respectively. Clinical success was achieved in 84.3 % with a median of 3 sessions (range: 1-22), with a higher rate in Barrett's neoplasia (89.7 % vs. 72 %, p = 0.042). Circumferential resection in one single procedure (13.2 %) was associated with the need for a higher number of dilation sessions. By multivariate analysis, upper-esophageal location (OR: 11.479 [95 % CI: 2.058-64.043], p = 0.005), recurrent strictures (OR: 17.252 [95 % CI: 2.833-105.069], p = 0.002), and dilation-related complications (OR: 26.420 [95 % CI: 1.736-401.966], p = 0.018) were risk factors of refractory stenosis.

Conclusion: patients presenting with SCC located in the upper superior esophagus, intra-procedural perforation, and recurrent strictures are at higher risk of developing refractory strictures.

Keywords: Endoscopic submucosal dissection. Endoscopic balloon dilatation. Esophageal stricture. Barrett's esophagus. Stenosis.

INTRODUCTION

Esophageal endoscopic submucosal dissection (ESD) is becoming increasingly common as a first-line approach for the treatment of Barrett's esophagus and squamous cell cancer (SCC) (1). Esophageal strictures can be a major complication with a critical impact on quality of life, and represent a clinical challenge. This adverse event may be more frequent in ESD (2). The circumference of the resected area and tumor size have been described as predictors of post-ESD strictures (3). Furthermore, oral administration of corticoids, proton pump inhibitors in Barrett's cases, local injections of triamcinolone (4) or steroid gel, antifibrotic agents (5), botulinum toxin (6), application of polyglycolic acid sheets (7), and early endoscopic balloon dilation (EBD) (8) have been proposed as useful preventive therapies.

Dilation therapy and local injection of corticoids should be the first-line treatment. Temporary stent placement (9,10), incisional therapy (11,12) and surgery may be other options (13). In addition, different etiologies of benign strictures may have a different natural history and response to EBD (14). Although clinical success is achieved in up to 93 % (14), a non-negligible proportion of these complex strictures can become refractory (15). The aims of the present study were to comparatively assess the outcomes in Barrett's esophagus and SCC, and to determine the factors associated with refractory post-ESD strictures.

METHODS

Patients

This was an observational, single-center, retrospective study. All consecutive patients from January 2007 to May 2016 with a post-ESD stricture who underwent ≥ 1 EBD were included. Previous radiofrequency ablation in Barrett's esophagus and oral therapy by corticoids following resection were noted. Patients with previous endoscopic dilations, esophageal surgery, confirmed motor disorders, or less than 3 months' follow-up after the last dilation were excluded. The study was approved by the institutional review board (2016/29DEC/1567). Individual informed consent was waived due to the retrospective design.

ESD technique and EBD

The ESD technique was carried out with curative intent using a dual knife (Olympus, Tokyo, Japan) as previously described (16,17). Underlying esophageal pathology, lesion's size (long axis), circumferential spreading, and number of resected specimens were collected. Proximal location was defined as the superior third of the esophagus.

Oral steroids were administered in patients with circumferential resections. An initial control endoscopy was performed either at 2 weeks in high-risk patients (resection extent > 75 %) or at any time of increasing dysphagia. Stricture was assessed by traversability with a conventional scope. EBD was performed in case of untraversability or increasing symptoms of dysphagia using a CRE wire-guided balloon (Boston-

Scientific, MA, USA) up to 1 minute with a maximum of 3 mm in a single session. Injection of corticoids was considered. Intra-procedural adverse events were collected. The indication of new dilation sessions was based on recurrent symptoms.

Definitions and outcomes

Symptomatic strictures were defined as follows: either untraversable strictures with a conventional endoscope or traversable strictures with increasing dysphagia. Dysphagia was evaluated in a qualitative fashion (yes/no) (18).

Technical success was defined as the completion of dilation (19). Clinical success was retained when dysphagia resolved, and the stricture could be traversed after < 5 dilation sessions over a 10-week period. On the contrary, a stricture was considered refractory if persistent dysphagia or untraversable after dilation therapy. The need for surgery, gastrostomy, or stent was also retained as a refractory stricture. Time to treatment success was the period between the first and last dilation sessions in patients with clinical success. The periodic dilation index was calculated by the number of dilations required over the duration of time to treatment success in months. A 12-month follow-up after the last EBD was considered (20). Recurrent stricture was defined as the inability to pass a standard diagnostic endoscope in a follow-up endoscopy after clinical success (13,19,21).

Statistical analysis

Categorical variables were compared using the χ^2 test. Normally distributed continuous variables were analyzed using Student's *t*-test, and non-normally distributed variables by the Mann-Whitney U-test. They were presented as mean ± SD or median (range), respectively. The factors associated with refractory strictures were assessed by multivariate logistic regression using the backward stepwise method. All significant features in the univariate analysis were included in the model. Time to treatment success was calculated using Kaplan-Meier curves and the log-rank test. Sample size was not calculated. A two-sided p-value < 0.05 was considered statistically significant. The SPSS v.25 package was used (IBM, IL, USA).

RESULTS

Patients and ESD procedure

Four-hundred and fourteen patients with SCC (n = 162) and Barrett's neoplasia (n = 252) underwent ESD. Eighty-three (20.1 %, mean age: 66 ± 11 yrs, 75.9 % men) who underwent 254 endoscopic dilations (median: 3, range: 1-27) because of post-ESD strictures were included**.** They had Barrett's neoplasia (n = 58, 69.9 %) or SCC (n = 25, 30.1 %). The resected lesions were located in upper (n = 11, 13.3 %), middle (n = 14, 16.9 %) and lower esophagus (n = 58, 69.9 %), and the median specimen size was 51 mm (22-110). Most of them were resected in en-bloc fashion (95.2 %). Oral steroids were given in 10 cases (12.1 %). Among patients presenting with Barrett's esophagus, there were 11 (19 %) with a resection in two times (16). There were patients with previous endoscopic mucosal resection (n = 3), radiotherapy (n = 4), and radiofrequency ablation (n = 13).

Dilation therapy and outcomes

As shown in table 1, the stricture length was shorter in the Barret's neoplasia group (20 mm vs. 30 mm, p = 0.004), although resected specimen's size was smaller in SCC. Overall, a ≥ 20 mm stricture length was observed in 57 patients (68.7 %). Technical success was achieved in all EBD procedures.

Clinical success was accomplished in 70 patients (84.3 %) by a median of 3 EBD (range: 1-22) in 5 weeks (range: 0-48), with a higher rate of clinical success in patients with Barrett's neoplasia (89.7 % vs. 72 %, p = 0.042). There were no differences in the time to clinical success between both groups (p = 0.700) (Fig. 1). Initial dilation was done a median of 22 days following ESD (6-60). There were 19 patients (24.7 %) with a "0 days" time to treatment success because they only need one EBD. The periodic dilation index was 2.3 dilatations/month. Concerning patients who required > 1 dilation, the median time to treatment success was 9 weeks. A 12-months follow-up free of symptoms after last EBD was achieved in 86.8 % of patients.

Patients with circumferential resection required more EBD sessions to clinical success (6 vs. 3, p = 0.045). In addition, the median endoscopic follow-up after endoscopic

resection and after last dilation were 31.5 (range: 6-118) and 25 months (range: 4-114). Overall, the complication per-patient rate was 4.8 %, including 4 perforations successfully treated by endoscopy.

Risk factors for refractory strictures

A refractory stricture was seen in 13 cases (15.7 %) due to insufficient luminal patency over a 10-week period (n = 6) or requiring stent placement (n = 1). There was no need for surgery.

Risk factors for refractory strictures are shown in table 2. Non-Barrett's lesions, upper esophageal location (Fig. 2), recurrent strictures, and intra-procedural complications were statistically associated with refractory strictures. Oral and local corticoids were associated with refractory strictures since they were used as salvage treatment during follow-up in these cases (Fig. 3). A median of 1 session (range: 1-5) of triamcinolone injection was performed in 15 cases. By multivariable analysis (Table 3), proximal location, recurrent strictures, and intra-procedural perforations were independent risk factors for refractory strictures. When adjusted by oral or local corticoid therapy, only recurrence and complications remain statistically significant.

Recurrence was observed in 9 cases (10.8 %) after a median of 14 weeks after first dilation and was associated with circumferential resections (36.36 % vs. 6.94 %, p = 0.003). Interestingly, there was no recurrent stricture in this subgroup when the circumferential resection was performed in two-steps.

DISCUSSION

In the present study we reported 83 patients who presented with post-ESD symptomatic esophageal strictures. Clinical success was achieved in 84.3 %. Refractory strictures were seen in 15.7 % of cases. SCCs, upper esophageal location, recurrent strictures, and intra-procedural complications were statistically associated with refractory strictures. Upper esophageal location was a risk factor for refractory strictures, even though tumor size and circumferential extension were larger in Barrett's esophagus. In this regard, the circumferential resection was associated with a higher number of EBD to achieve clinical success.

The downside of esophageal ESD is indeed the high stricture risk that occurs due to the wound healing process because of the epithelial defect. The post-ESD stenosis rate ranges from 7-18 % (22). In our series a 20.1 % stricture rate was observed, probably due to a high rate of ≥ 75 % of circumferential dissection (50.6 %). A stricture risk up to 70-90 % has been reported when post-ESD mucosal defects of > 3/4 of the circumference (23,24).

In our study, complete circumferential resection in one single procedure was associated with a higher number of EBD. Conversely to other studies (25), in our series there was no association with refractory strictures, probably because we administered oral corticosteroids.

These high stricture rates result in high morbidity rates, where patients will suffer of dysphagia and will need to undergo multiple dilatation sessions. Along with patient discomfort, these dilation sessions are associated with an increased risk of perforation (26,27). Our perforation rate (4.5 %) during dilation therapy was lower than previously published (27), and all complications were managed conservatively. This subgroup of patients may however require specific management, individualizing the timing of EBD sessions and further therapies. Most patients with dilation-related complications developed refractory strictures supposedly due to the wall damage and inflammation and needed further stent placement or multiple balloon dilation sessions.

The role of steroids in the treatment of refractory strictures could not be assessed in our study, since steroids were used either as prevention in circumferential resections or as concomitant therapy in refractory cases. To reduce the stricture rate, various preventative strategies have been investigated (7,23). Standard prevention involves the anti-inflammatory and anti-fibrotic properties of steroid treatment that have shown promising results in multiple studies. Intra-lesional triamcinolone injections, with varying dosages and varying increments of endoscopic administration, have shown a stricture reduction of 25-56 % (28,29) as a promising stenosis-preventive therapy (30). Oral steroids, generally administered for 8 weeks starting at a dosage of 30 mg/day tapering gradually, show similar stricture reduction rates varying from 26.7-51.1 % after ESD (31-33). In our study, the preventive role of steroids could not be assessed since it has been used as prevention and treatment of strictures. Extensive

and circumferential resection was not associated to refractory strictures.

Of note, we included patients with lesions of various types and sizes, while most studies in the literature report on Barrett's esophagus or SCC separately. This approach facilitates the comparison of post-ESD strictures between both groups and assesses the global risk factors. In our series, multivariable logistic regression analysis suggested that proximal location was an independent factor associated with refractory strictures. Patients with SCC had significantly smaller resected specimens (46 mm vs 60 mm) but longer strictures lengths (30 vs 20 mm), despite a complete circumferential resection rate comparable to that of Barrett's neoplasia. The proximal esophagus has a lower lumen diameter and strictures may be complex (asymmetric) and poorly tolerated. Furthermore, other concomitant treatments such as radiotherapy may increase the risk of post-ESD strictures or recurrence. SCC located in the middle esophagus may have the same risk for refractory stenosis as does distal Barrett's esophagus. Intra-procedural complications and recurrence were also independent risk factors of refractory patients. Nevertheless, the OR confidence intervals were wide, probably because of the low number of patients presenting with these risk features, and therefore the results should be interpreted cautiously.

This study has several limitations. We included a heterogeneous group of patients who underwent other concomitant therapies such as oral or injected corticoids. For this reason, we adjusted the multivariable analysis for corticosteroid therapy. There were no fixed follow-up check points to assess dysphagia or EBD response. Moreover, the degree of dysphagia was not evaluated and the interval between dilation sessions was based on endoscopist preferences and the clinical symptoms. Finally, the exact number of patients excluded of the study because of esophageal surgery or confirmed motor disorders was unknown and this can lead to a selection bias.

In conclusion, patients presenting with SCC located in the upper superior esophagus, intra-procedural perforation, and recurrent strictures are at higher risk of developing refractory strictures. Preventive strategies, concomitant treatment, and dedicated dilatation protocols should be considered and undertaken in these patients. These features can also lead to longer times for treatment success.

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Table 1. Patient baseline characteristics

Feature	**Barrett's neoplasia (n = 58)**	**SCC (n = 25)**	**p-value**
Male gender	49 (84.5 %)	9 (45 %)	0.005*
Age (mean ± SD, years)	66 ± 12	65 ± 8	0.855
Circumference resection ≥ 75 %	34 (58.6 %)	8 (32 %)	0.026*
Circumference resection 100 %	7 (12.1 %)	4 (16 %)	0.628
Specimen's size (median, range, mm)	60 (25-110)	46 (22-104)	0.002*

Stricture length (median, range, mm)	20 (5-70)	30 (10-70)	0.004*
Non-traversable stricture	29 (50 %)	17 (68 %)	0.130
Early (≤ 15 days) dilation	14 (24.1 %)	4 (16 %)	0.409
Intra-procedural complications (per patient)	3 (5.2 %)	1 (4 %)	1
Clinical success	52 (89.7 %)	18 (72 %)	0.042*
Maximum dilation (median, range, mm)	18 (15-20)	15 (8-18)	< 0.001*
Number of EBD to clinical success (median, range)	3 (1-12)	2 (1-22)	0.132
Time to clinical success (median, range, weeks)	6 (0-48)	2 (0-34)	0.277
Number of EBD to last dilation (median, range)	4 (1-17)	3 (1-27)	0.574
Time to last dilation (median, range, weeks)	6 (0-307)	12 (0-132)	0.901
Refractory stricture	6 (10.3 %)	7 (28 %)	0.042*
Recurrent stricture	7 (12.1 %)	2 (8 %)	0.584
12-month follow-up free of symptoms	55 (94.8 %)	17 (68 %)	0.001*

*Statistically significant. EBD: endoscopic balloon dilation; ESD: endoscopic submucosal dissection.

Table 2. Univariate analysis of risk factors for refractory strictures

Feature	***n* (%)**	**Refractory rates**	***OR (95 % CI)***	***p-value***
Male gender	63 (75.9 %)	15.9 % vs. 15 %	1.069 (0.263-4.341)	0.925
Age ≥ 65 years	48 (57.8 %)	20.8 % vs. 8.6 %	2.807 (0.711-11.082)	0.129
Squamous cell carcinoma/ Barrett's esophagus	58 (69.9 %)	28 % vs. 10.3 %	2.707 (1.011-7.244)	0.048*
Proximal location	11 (13.3 %)	45.5 % vs. 11.1 %	6.667 (1.651-26.926)	0.004*
Hybrid approach/standard ESD	4 (4.8 %)	25 % vs. 15.19 %	1.861 (0.178-19.419)	0.501
More than 1 ESD session	11 (13.3 %)	0 % vs. 100 %	-	0.125
Circumference resection ≥ 75 %	42 (50.6 %)	16.7 % vs. 14.6 %	1.167 (0.356-3.823)	0.799
Circumference resection 100 %	11 (13.3 %)	27.3 % vs. 13.9 %	2.325 (0.526-10.270)	0.255
Specimen size ≥ 50 mm	53 (65.4 %)	15.1 % vs.17.9 %	0.818 (0.24-2.784)	0.747
Stricture length ≥ 20 mm	57 (68.7 %)	21.1 % vs. 3.9 %	6.667 (0.818-54.319)	0.045
Non-passable stricture	37 (44.6 %)	21.7 % vs. 8.1 %	3.148 (0.798-12.423)	0.089
Local corticoids	15 (18.1 %)	40 % vs. 10.3 %	5.81 (1.59-21.225)	0.004*
Oral corticoids	10 (12.1 %)	50 % vs. 10.4 %	8.125 (1.924-34.32)	0.001*
Early (≤ 15 days) dilation	18 (21.7 %)	16.7 % vs. 15.4 %	1.100 (0.268-4.51)	0.895

Recurrent stricture	9 (10.8 %)	55.6 % vs. 10.8 %	10.313 (2.288-46.480)	< 0.001*
Radiofrequency ablation	13 (15.7 %)	15.4 % vs. 15.7 %	0.975 (0.189-5.019)	0.976
Intra-procedural complications	4 (4.8 %)	75 % vs. 12.7 %	20.7 (1.958-218.869)	0.011*

*Statistically significant. ESD: endoscopic submucosal dissection; OR: odds ratio; CI: confidence interval.

Table 3. Multivariate logistic regression analysis to determine independent risk factors for refractory strictures

Risk factor	***OR (95 % CI)***	**p**	***OR (95 % CI)*[a]**	**p[a]**	***OR (95 % CI)*[a2]**	**p[a2]**
Proximal location	11.479 (2.058-64.043)	0.005*	-	-	-	-
Recurrent	17.252 (2.833-105.069)	0.002*	15 (2.258-99.639)	0.005*	10.165 (1.396-74)	0.022*
Intra-procedural perforations	26.420 (1.736-401.966)	0.018*	40 (2.782-575.201)	0.007*	22.421 (1.362-369.107)	0.030*

*Statistically significant. OR: odds ratio; CI: confidence interval. [a]Adjusted for administration of oral corticoids (no); [a2]Adjusted for injection of triamcinolone (no).

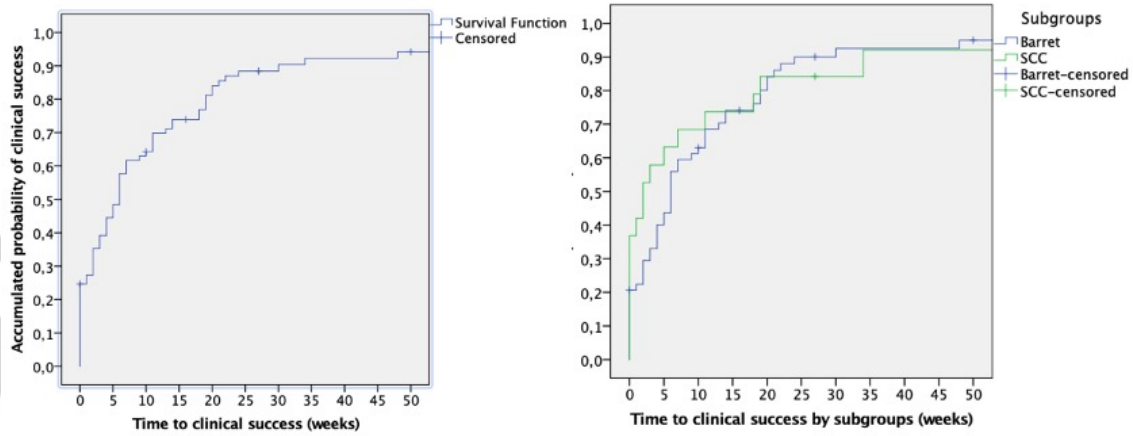

Fig. 1. The median survival time to treatment success of endoscopic balloon dilation in

post-endoscopic submucosal dissection strictures was 6 weeks, with no differences between the Barrett's esophagus and squamous cell carcinoma groups.

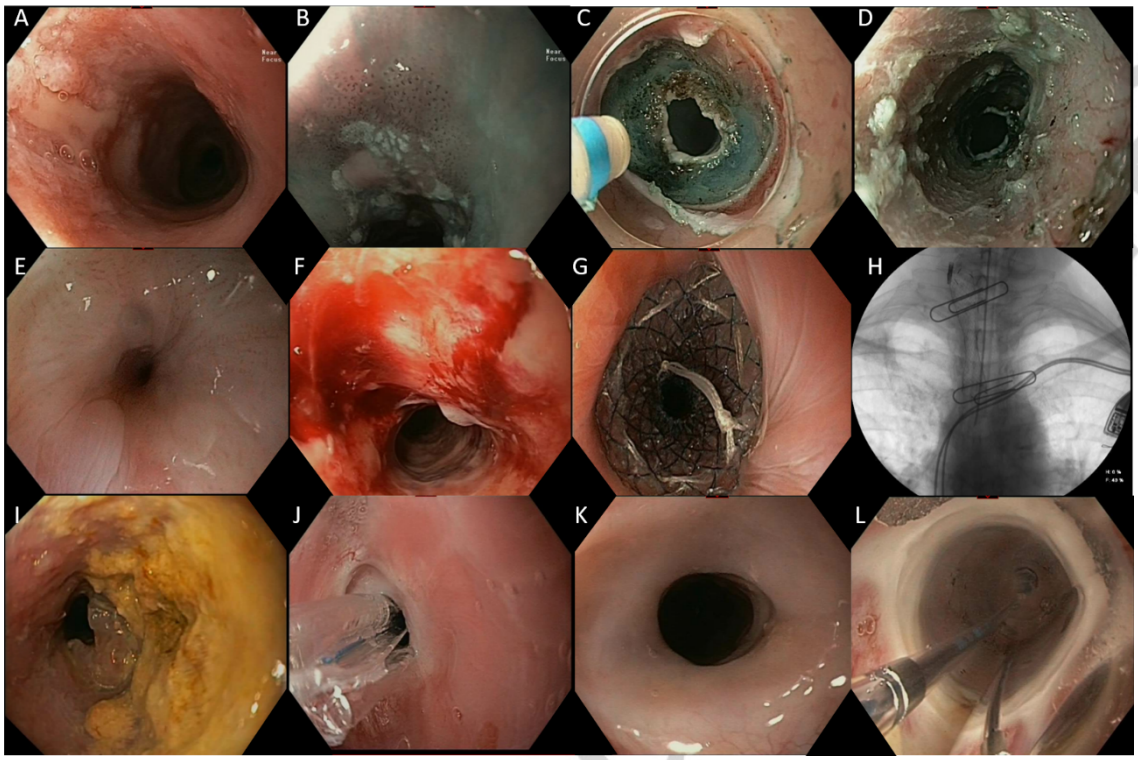

Fig. 2. Refractory stricture after circumferential endoscopic submucosal dissection (ESD) for squamous cell carcinoma (SCC). Multifocal SCC pT1sm1 extending > 80 % of the circumference (A, B). R0 resection (C: distal incision; D: length of resection 5 cm). Post-ESD stricture at 2 months treated by dilation (E). A perforation (F) treated by stenting (G, H), removed after 4 weeks (I). Recurrent stricture (J), needing up to 10 dilations (K, L).

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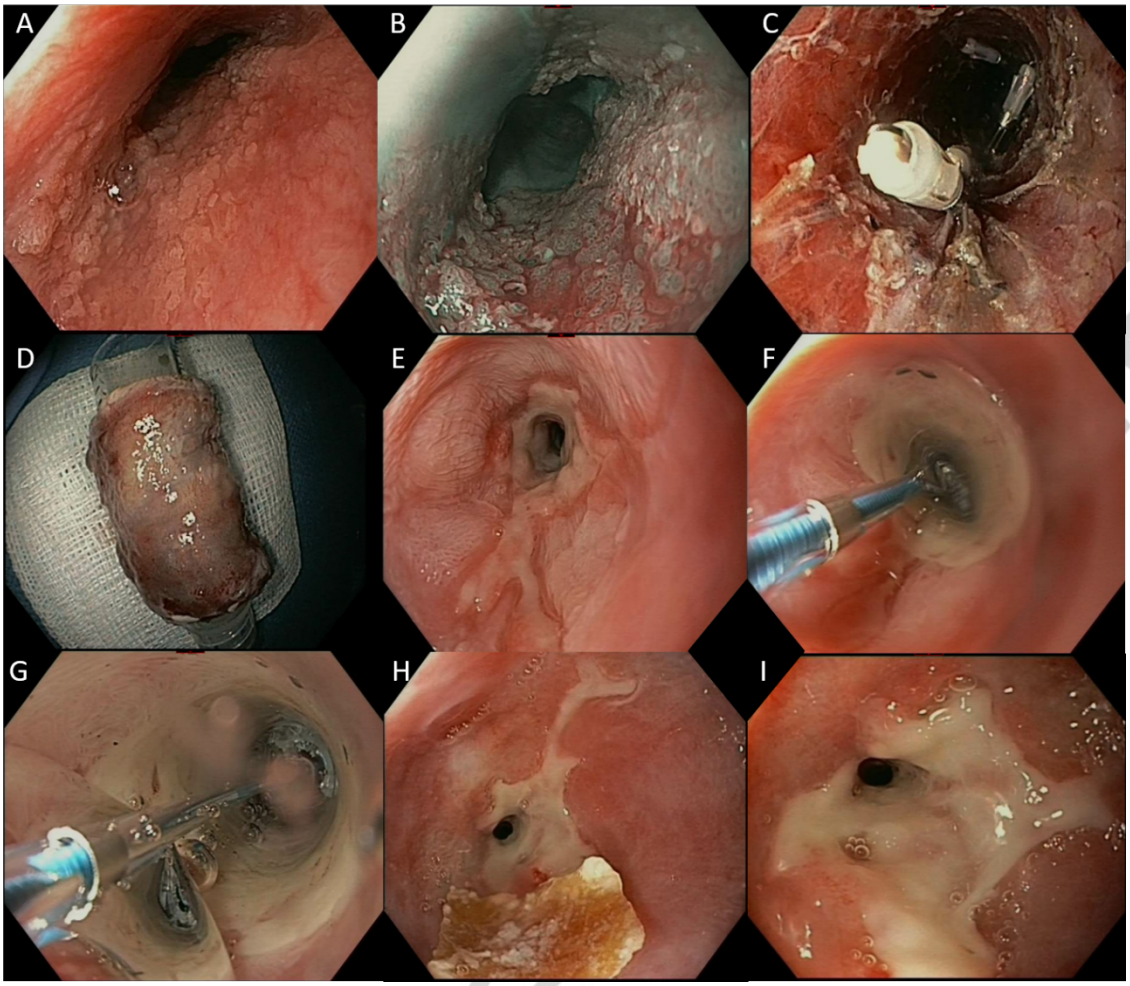

Fig. 3. Refractory stricture after circumferential endoscopic submucosal dissection for squamous cell carcinoma (SCC) pT1m3, despite oral steroids. SCC involving the upper esophagus (A, B); R0 resection (C, D); dysphagia and stricture at 2 months of follow-up, dilated up to 6 times (E-G); 18 months of follow-up (H, I).