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Is a higher frequency of esophageal dilations more effective in treating benign esophageal strictures? Retrospective, multicenter study

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Authors
Christiana Graf[1], Monika Reden[1], Tobias Blasberg[2], Mate Knabe[1], Andrea May[3], Christian Ell[2], Edris Wedi[2], Nils Wetzstein[4], Florian Michael[1], Stefan Zeuzem[1], Jörg Bojunga[1], Mireen Friedrich-Rust[1]

Institutions
1 Department of Internal Medicine I, Hospital of the Goethe University Frankfurt, Frankfurt am Main, Germany
2 Department of Gastroenterology, Sana Klinikum Offenbach, Offenbach, Germany
3 Department of Gastroenterology, Asklepios Klinik Wiesbaden, Wiesbaden, Germany
4 Department of Infectious Diseases, Hospital of the Goethe University Frankfurt, Frankfurt am Main, Germany

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Corresponding author
Dr. Christiana Graf, Hospital of the Goethe University Frankfurt, Department of Internal Medicine I, Frankfurt am Main, Germany
christiana.graf@kgu.de

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ABSTRACT

Background and study aims There is still a lack of evidence-based recommendations concerning endoscopic bougienage in benign esophageal strictures. Our study aimed to assess the relevance of the time interval between endoscopic dilation (ED) sessions with regard to endoscopic and clinical response.

Patients and methods We performed a retrospective study including patients treated with endoscopic bougienage for a benign esophageal stricture in two German centers. Primary endpoint was the number of ED until freedom from dysphagia was achieved. Secondary endpoints were analyses on reaching a diameter of 15 mm and on achieving clinical freedom from symptoms.

Results Between April 2014 and March 2020, bougienage was used as the primary treatment for benign esophageal strictures in 238 patients (194 patients in Center 1; 44 patients in Center 2). Both centers differed in their endoscopic bougienage regime: Center 1 was characterized by a higher frequency of interventions compared to Center 2 (median: 2 days [range 1–28] vs. 10 days [range 1–41]; $P<0.001$). Clinical response was achieved significantly earlier using the high-frequency regimen in all patients except for those with post-radiogen strictures, who clinically benefited from a low-frequency ED program. Accordingly, patients receiving higher-frequency ED reached a significantly larger post-dilation diameter and considerably larger diameter differences.

Conclusions The results of our study demonstrate that a treatment concept consisting of higher-frequency bougienages seems to be more effective in treating most types of esophageal stricture. Radiogenic strictures were the only types of stenoses that benefited from a lower frequency ED program.

Introduction

Benign esophageal strictures can be challenging to treat and 30% to 40% of them recur despite rigorous endoscopic dilations (EDs) [1]. They are defined by any abnormally stenotic segment of the esophagus and are called as refractory when there is a failure to maintain luminal patency after at least five EDs [2]. Clinically, esophageal strictures are manifested by dysphagia, commonly described by patients as difficulty to swallow. By far the most common cause of benign esophageal strictures is gastroesophageal reflux disease (GERD, peptic stricture), accounting for at least 80% of cases [3, 4]. Beyond that, most cases of benign esophageal strictures derive from eosinophilic esophagitis, from endoscopic therapy, radiation injury, anastomotic formations after surgical interventions, drug-induced esophagitis, and corrosive substance ingestion [5].

In the last decades new technological advances in endoscopic therapy of esophageal strictures have shown promising results with notable improvement in stricture management, low recurrence rates and fewer complications. The techniques most utilized for benign strictures management include through the scope balloons or bougies [1]. Studies comparing the efficacy of bougies and endoscopically-directed balloons for the dilation of benign strictures have shown a comparable efficacy and complication rates of both procedures [6, 7, 8, 9]. The goal of endoscopic intervention for patients with nonmalignant esophageal strictures is relief of dysphagia by increasing the diameter of the esophageal lumen. Due to a large inter-individual variability, there is no general correlation between the maximum luminal diameter and clinical response. However, data and clinical experience have suggested that dilation to a lumen diameter of 15 to 17 relieves patients from dysphagia [10].

Unfortunately, there is a paucity of data concerning the evaluation of the optimal number of dilations as well as the optimal frequency of endoscopic sessions and evidence-based recommendations are lacking. This lack of published data is particularly striking because endoscopic bougienage has gained great popularity and relevance in treating benign esophageal strictures. The goal of our study was to compare two different concepts of ED concerning the frequency of interventions in two endoscopic centers with regard to endoscopic results and clinical response. Both centers differed in the time intervals between two EDs with one of them showing a higher frequency of dilations whereas the second center was characterized by a longer period of time between two bougienages.

Patients and methods

In this retrospective study, adult patients aged 18 and over who were treated at the participating hospitals (Center 1: Sana Klinikum Offenbach; Center 2: University Hospital Frankfurt) for esophageal dilatation using the bougienage technique with Savary-Gilliard dilators between April1, 2014 and March 1, 2020 were included in the study. Possible patients were identified by systematically searching the patient chart database of the participating hospitals for bougienage related Operation Procedure codes (OPS) 5–429.7 and 5–429.8.

Medical records of the resulting cases were systematically reviewed. The diagnosis of a benign esophageal stricture was based on typical radiologic, endoscopic appearance and on negative biopsies for malignancy. Esophageal stricture was defined by obstruction of the esophageal lumen by at least 50% as a result of benign disease and complaint of dysphagia. Stricture diameter was determined by the diameter of the first bougie or balloon used in an ED session. Size of dilation was determined from the first to the last bougie or balloon used in one ED session. Patients treated by balloon dilatation were excluded from analysis.

Extracted patient data included baseline characteristics (gender, age), stricture characteristics (etiology, localization, length, complexity), ED characteristics (procedure date, number of interventions, pre- and post-dilation diameter), adverse events (AEs) related to ED and duration of follow-up. For single stricture characteristics, data were not always available for all patients. Thus medians, ranges, and percentages were always calculated based on the corresponding available data, which were in Center 1 as follows: stricture length, n = 141; stricture complexity, n = 188. Corresponding available in Center 2 were as follows: stricture length, n = 39; stricture complexity, n = 44.

The primary endpoint was defined as the number of Savary dilations until freedom from dysphagia was achieved. Beyond that, we assessed the number of therapeutic episodes until long-term freedom from dysphagia was achieved. Further clinical endpoints were the time span until freedom from dysphagia was observed and the duration of freedom from dysphagia, which was defined as the time span between the last ED, which was necessary to achieve freedom from dysphagia, and the time point of the first ED, which was carried out due to recurrence of dysphagia. For conducting regression analysis, reaching freedom from dysphagia by a low number of ED sessions (≤4) was defined as clinical endpoint.

Concerning endoscopic endpoints, we assessed the maximal post-dilation diameter. Beyond that, we analyzed the difference in pre-dilation and post-dilation diameter and the number of patients who achieved and did not achieve a dilation diameter of 15 mm. The time as well as the number of ED sessions until a dilation diameter of 15 mm or – in cases of not reaching a dilator size of 15 mm – until the alternative maximal dilation diameter was achieved was recorded in both groups. Clinical endpoints comprised the time as well as the number of ED sessions and the number of treatment episodes until permanent freedom from dysphagia was achieved. One therapy episode was defined by the temporal sequence of endoscopic interventions, which were no more than 3 months apart.

Additional endpoints included AEs, which were defined as events which were related to ED and required consecutive endoscopy or hospitalization. Hemorrhage was defined as observed esophageal bleeding after ED session. Esophageal perforation was defined as a rupture of the esophageal wall after bougienage. Retrosternal pain was defined as retrosternal noncardiac chest comfort. The presence of ulcer was defined as a discrete postinterventional break in the esophageal mucosa.

This study was approved by the local ethics committee of the Goethe University Frankfurt (vote #2021–97). Patients were excluded if they were younger than 18 years old or pregnant. Owing the retrospective, anonymous nature of the study, no informed consent from individual patients had to be obtained.

Procedure

Due to the retrospective nature of the study, endoscopic procedures were not standardized. Nevertheless, both participating centers complied with the guidelines for ED in clinical practice [5, 11]. During the endoscopic procedure, patients received conscious sedation, deep sedation or general anesthesia with an endotracheal tube, depending on the treating physicians' discretion. ED was performed using wire-guided bougies (mainly Savary-Gilliard bougies, Cook Medical, Bloomington, Indiana, United States) in both centers. There is no general correlation between maximum diameter and clinical response and accordingly no consensus on the definition of an endpoint for dilation therapy. However, a case series of 321 patients showed that reaching a diameter of 15 mm was associated with clinical response and freedom from symptoms in 98% of cases [12].

Accordingly, international guidelines also recommend weekly or two-weekly dilatation sessions until easy passage of a ≥15-mm dilator is achieved [5]. Thus, successful therapeutic bougienage was defined when the dilator of 15 mm was effectively passed and complete resolution of dysphagia was noted by the patient. Follow-up was conducted until patients were permanently symptom-free and did not require further dilations.

Statistical analysis

Statistical analyses were performed using IBM SPSS 26.0 statistical software package (SPSS/IBM, Munich, Germany). Characteristics of the cohort were examined by descriptive statistics (percentages, means, standard deviation, etc.). Categorial variables were compared using the chi-square or Fisher exact test, as appropriate, and expressed as frequencies and percentages. Variables showing $P<0.05$ in the univariate model were analyzed in a multivariate logistic regression model. Odds ratio (ORs) and 95% Cis were calculated for the independent predictive factors of SVR. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Version 22 and R (Version 4.0.4).

Results

The main baseline patient characteristics of the overall study population, including demographic and clinical features are listed in ▶ **Table 1**. Between April 2014 and March 2020, bougienage was used as the primary treatment of benign esophageal stricture in 238 patients (194 patients in Center 1 and 44 patients in Center 2). All of these patients presented with solid food dysphagia and an upper gastrointestinal endoscopy was performed in all cases, which ensured the diagnosis of benign esophageal stenosis. The majority of benign esophageal strictures of Center 1 derived from GERD (30.9%) and iatrogenic from endoscopic therapy (endoscopic mucosal resection [EMR]), argon plasma coagulation [APC] or radiofrequency ablation [RFA]; 27.8%). Benign esophageal strictures at Center 2 were primarily characterized by radiogenic (50.0%) and peptic nature (16.0%). One hundred seventeen patients in Center 1 (60%) and eight patients (18%) in Center 2 were treated with high-dose proton-pump inhibitor (PPI) therapy after endoscopic dilatation to reduce recurrence rate. Standard-dose PPI therapy was administered to 54 patients (0.5%) at Center 1 and 2 patients (5%) at Center 2, respectively. Post-therapeutic stenoses after EMR were treated with high-dose PPI therapy according to a specific protocol consisting of 3×40 mg PPI over 3 weeks followed by therapy with 2×40 mg PPI until the patient presented again.

Post-radiation strictures derived in both centers from radiotherapy treatment of solid organ malignancies. In most cases, patients were treated for esophageal or head and neck cancer (Center 1: esophageal cancer, n = 8, head and neck cancer, n = 7; Center 2: esophageal cancer, n = 5; head and neck cancer, n = 15), followed by lung cancer (Center 1: n = 3; Center 2: n = 0), lymphoma (Center 1: n = 1; Center 2: n = 1) and multiple endocrinological neoplasia (Center 2: n = 1).

The centers differed in their endoscopic bougienage regime: Cohort 1 was characterized by a higher frequency of interventions and a shorter period of time between ED sessions: median duration between two interventions were 2 days (1–28) in Cohort 1 compared to 10 days (1–41) in Cohort 2 ($P<0.001$).

Follow-up was available in all of the patients until permanent freedom from dysphagia was achieved. Median duration of follow-up from the beginning of ED using bougienage to the last follow-up, which was marked by freedom from symptoms, were 155 days (range 0, 1792) in Center 1 and 186 days (range 0, 4107) in Center 2.

Clinical response

Concerning the clinical response, significantly fewer ED sessions were necessary using the therapeutic regimen at Center 1 until patients presented permanently symptom-free (▶ **Table 2**; ▶ **Fig. 1a**). In line with these findings, the time until patients were permanently free of dysphagia was shorter and the time span in which patients presented free of dysphagia was longer in patients in Cohort 1 compared to those in Cohort 2 (99 vs. 95; $P = 0.88$; 162 vs. 191, $P = 0.35$; ▶ **Table 2**; ▶ **Fig. 1b,c**). Only the number of therapy episodes required to achieve permanent freedom from symptoms was significantly higher in patients treated in Center 1 (2 vs. 1, $P = 0.01$; ▶ **Table 2**; ▶ **Fig. 1d**).

Endoscopic outcome

Evaluating the effectivity of higher- versus lower-frequency ED at both centers with regard to endoscopic outcomes, Cohort 1 reached significantly larger maximum dilation diameters (Cohort 1: 15, Cohort 2: 14; $P<0.001$; ▶ **Fig. 2a**). Accordingly, reaching a dilator size of 15 mm as one further endoscopic outcome was observed significantly more frequently in Cohort 1 (81.4% vs. 50%, $P<0.001$; ▶ **Table 2**). Moreover, the time as well as the required total number of EDs until a dilator size of 15 mm was achieved were also significantly shorter and lower in Cohort 1 compared to Cohort 2 (62 vs. 213 days, $P<0.001$; 3 vs. 9

▶ **Table 1** Baseline characteristics.

Characteristics	Center 1*	Center 2*	*P*
Patients, n (%)	194	44	
Patient age at diagnosis(years), mean ± SD	70 ± 1.0	61 ± 3.2	0.06
Male gender, n (%)	143 (73.7)	22 (65.6)	0.51
Localization of esophageal stenosis, n (%)			
Proximal esophageal stricture	42 (21.6)	25 (56.8)	<0.001
Mid-esophageal stricture	43 (22.2)	7 (15.9)	0.27
Distal esophageal stricture	77 (39.7)	11 (25.0)	0.04
Elongated stricture	26 (13.4)	1 (2.3)	0.39
Characterization of esophageal stricture, n (%)			
Simple, n (%)	35 (19)	4 (9)	0.14
Complex, n (%)	153 (81)	40 (91)	0.14
Multiple, n (%)	7 (4)	1 (2)	1.00
Short (<2 cm) (%)	59 (42)	14 (35)	1.00
Long (≥2 cm) (%)	82 (58)	26 (59)	0.76
Stricture length, median (range)	3 (0.5–23)	2 (1–5)	0.04
Cause of esophageal stricture, n (%)			
Peptic	70 (36.0)	10 (22.7)	0.31
Post-radiation	19 (9.8)	22 (50.0)	<0.001
Eosinophilic esophagitis	4 (2.1)	1 (2.3)	0.57
Anastomotic stenosis	14 (7.2)	3 (6.8)	0.99
Corrosive	2 (1.0)	1 (2.3)	0.26
Post-therapeutic after EMR-/APC therapy or RFA	54 (27.8)	2 (4.5)	<0.001
Pseudodiverticulosis	8 (4.1)	0 (0)	0.41
Desquamative esophagitis	1 (0.5)	0 (0)	0.56
Papillomatosis	1 (0.5)	0 (0)	0.56
Others	3 (1.5)	4 (9.1)	0.006
Cause not defined	9 (4.6)	2 (4.5)	0.65

APC, argon plasma coagulation; EMR, endoscopic mucosal resection; RFA, radiofrequency ablation; SD, standard deviation.
*Center 1: University Hospital Frankfurt; Center 2: Sana Klinikum Offenbach.

ED, *P*<0.001; ▶**Table 2**; ▶**Fig. 2b,c**). In 22% of patients from Center 1 and 50% of patients from Center 2, a dilator size of 15 mm could not be achieved. Comparing those subgroups with each other, the alternative maximal dilator size in Cohort 1 was also larger than in Cohort 2 (14 vs. 12; *P* = 0.114; ▶**Table 2**). Moreover, the time span and the total number of ED required to achieve the alternative maximum dilator size were significantly shorter and lower in patients from Center 1 as well (2 vs. 60 days, *P*<0.001; 2 vs. 4 ED, *P* = 0.03; ▶**Table 2**, ▶**Fig. 3a,b**).

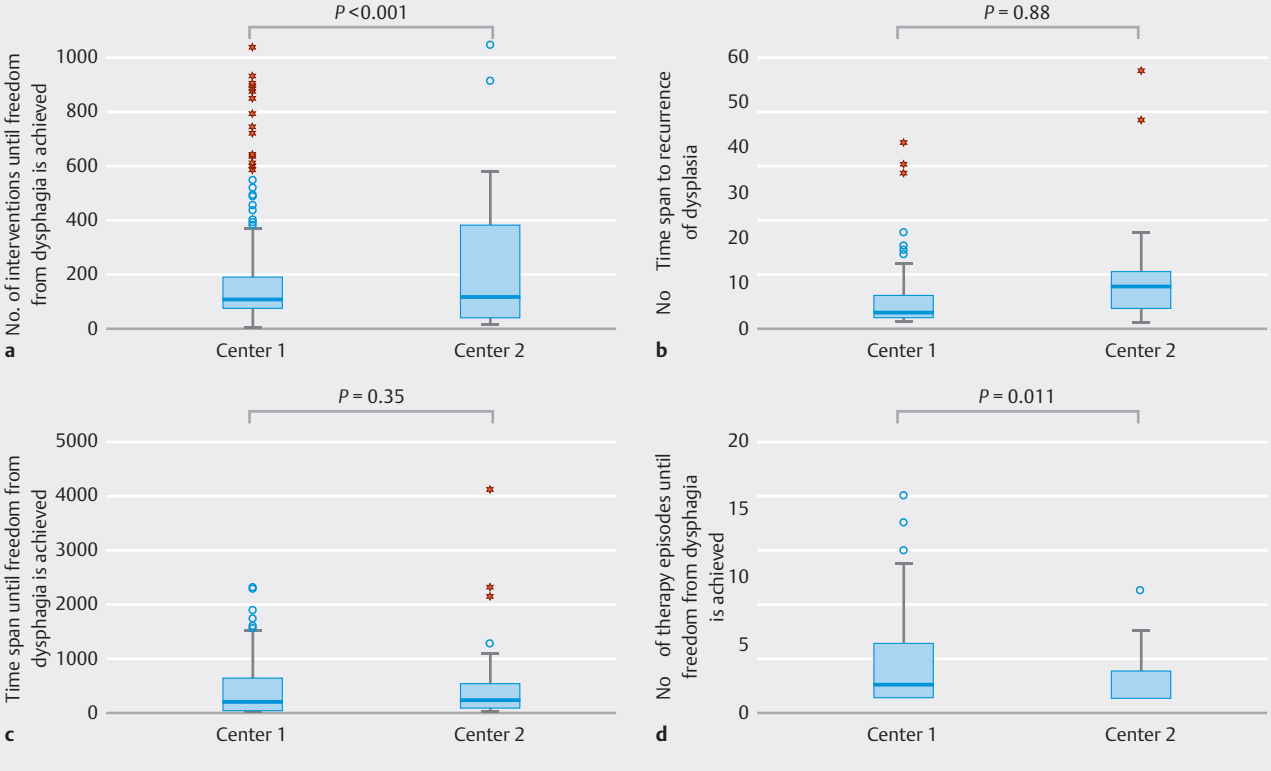
Previous data have shown that reaching a dilation diameter of 16 mm after the first three ED sessions was associated with fewer ED sessions during follow-up until freedom from dysphagia was achieved [13]. Analyses in our study cohort showed that 122 patients of Center 1 and 10 patients of Center 2 reached a post-dilation size of 16 mm (*P*<0.001). Moreover, a dilation up to 16 mm after the first three ED sessions was achieved in one patient at Center 2 and in 83 patients at Center 1 (*P*<0.001).

Finally, we conducted logistic regression analysis in order to identify independent predictors of endoscopic and clinical endpoints. At PP univariate analysis, different bougienage concepts of both centers (*P*<0.001) and age (*P* = 0.04) were significantly associated with achieving a dilator size of 15 mm. A following multivariable analysis revealed that the different bougienage regimens of both centers were the only independent predictive factor of reaching a dilator size of 15 mm (OR = ; *P* = 0.003). Regarding clinical response, again the different bougienage regi-

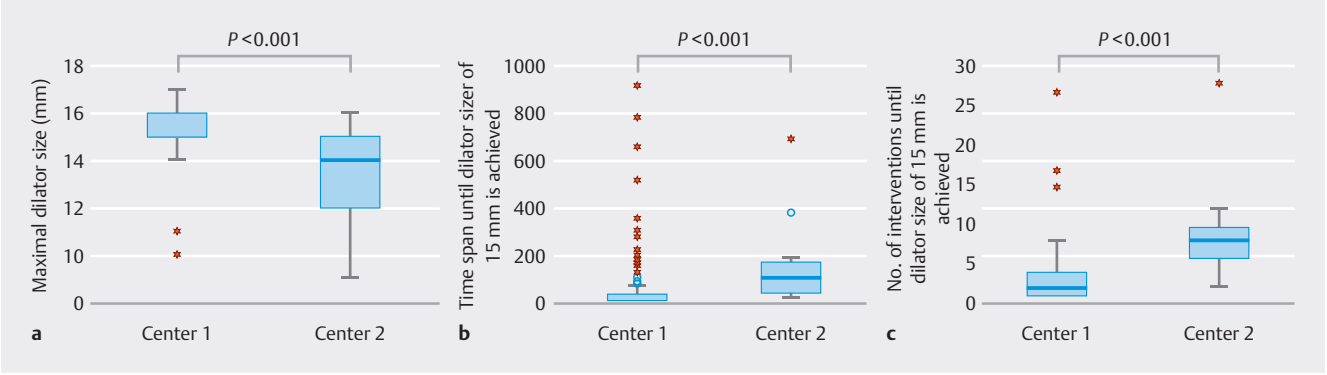
▶ **Table 2** Effect of bougienage on clinical and endoscopic endpoints.

Endpoints	Center 1*	Center 2*	*P*
Clinical endpoints			
Time span until freedom of dysphagia was achieved (months), median (range)	155 (0–1792)	186 (0–4107)	0.35
No. of Savary dilations until freedom from dysphagia was achieved, median (range)	3 (1–41)	9 (1–57)	<0.001
No. of therapy episodes containing Savary dilations until long-term freedom of dysphagia was achieved, median (range)	2 (1–16)	1 (1–9)	0.011
Time span to recurrence of dysphagia, median (range)	99 (1–1042)	95 (5–1003)	0.88
Endoscopic endpoints			
Predilator size, median (range)	9 (5–15)	7 (5–12)	<0.001
Maximum dilator, median (range)	16 (10–18)	14 (9–16)	<0.001
Difference in dilation diameter, median (range)	8 (3–15)	7 (0–10)	0.30
Dilator size of 15 mm is achieved, n (%)	158 (81.4)	22 (50.0)	<0.001
Time span until dilator size of 15 mm was achieved (days), median (range)	2 (0–1743)	73 (0–750)	<0.001
No. of Savary dilations until dilator size of 15 mm was achieved, median (range)	2 (1–27)	8 (2–28)	<0.001
Dilator size of 15 mm is not achieved, n (%)	36 (18.6)	22 (50.0)	
Time span until maximal dilator size was achieved (days), median (range)	41 (0–706)	60 (0–648)	0.001
No. of Savary dilations until maximal dilation size was achieved, median (range)	2 (1–22)	4 (1–12)	0.03

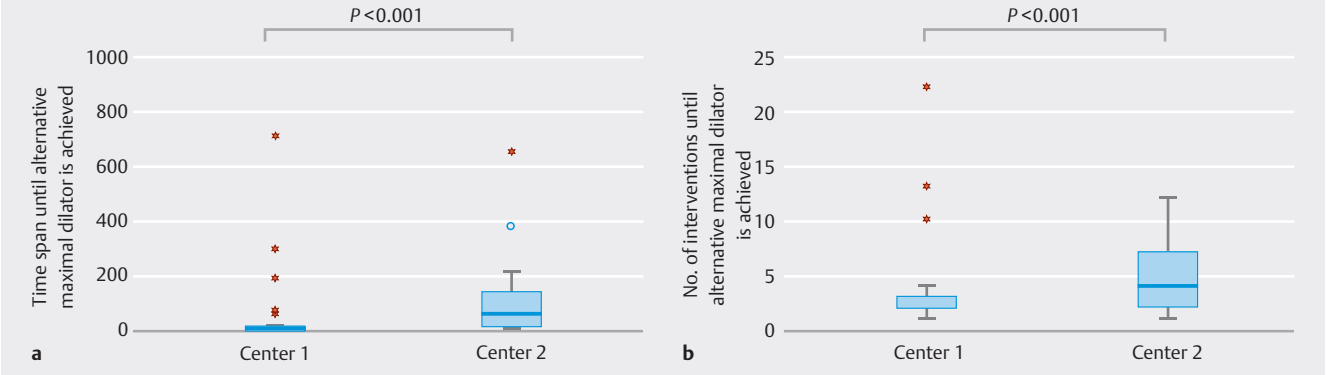
*Center 1: University Hospital Frankfurt; Center 2: Sana Klinikum Offenbach.



▶ **Fig. 1** Comparison of endoscopic concepts of both centers regarding **a** maximum dilator size, **b** the time span until a dilator size of 15 mm was achieved and **c** the number of interventions until a dilator size of 15 mm was achieved. The top and the bottom of the boxes are the first and the third quartiles, respectively. The length of the box thus represents the IQR within which 50% of the values were located. The line through the middle of each box represents the median. The error bars show the minimum and maximum values (range).



▶ **Fig. 2** Comparison of endoscopic concepts of both centers regarding **a** the time span until the maximal alternative dilator size<15 mm was achieved and **b** the number of interventions until the maximal alternative dilator size<15 mm was achieved. The length of the box thus represents the IQR within which 50% of the values were located. The line through the middle of each box represents the median. The error bars show the minimum and maximum values (range).



▶ **Fig. 3** Comparison of endoscopic concepts of both centers regarding **a** the number of interventions until freedom from dysphagia is achieved, **b** the time span until freedom from dysphagia is achieved, **c** the duration of freedom from symptoms until dysphagia recurred and **d** the number of therapy episodes until freedom from dysphagia is achieved. The length of the box thus represents the IQR within which 50% of the values were located. The line through the middle of each box represents the median. The error bars show the minimum and maximum values (range).

mens of each center (P<0.001) and stricture localization (P= 0.008) were identified as independent predictive factors of achieving freedom from dysphagia by a low number of ED sessions (≤4) in a per protocol analysis. A consecutive multivariate analysis revealed that again only the bougienage concept of each center turned out to be an independent predictive factor of achieving freedom from dysphagia by a low number (≤4) of ED sessions (P = 0.002).

ED-related adverse events

A total of 62 AEs (26.1%) requiring repeat endoscopy or hospitalization were recorded in both centers (**Appendix Table 1**). The most common AE after an ED session was hemorrhage in Center 1 (11.9%) and retrosternal pain in Center 2 (20.5%). Serious AEs such as gastric perforation or esophageal ulcer after bougienage were observed to be rare. No patients died from an ED-related cause. Regarding the incidence of peri-intervention and post-intervention AE, no significant difference could be observed between the centers.

Subanalyses of clinical and endoscopic outcomes depending on the localization and etiology of esophageal strictures

Both study cohorts were heterogenous regarding the frequencies of localization and the type of stricture. Moreover, predilator size was significantly smaller in Cohort 2 compared to that of Cohort 1 (P<0.001; ▶ **Table 2**). Thus, to better draw comparisons and to avoid selection bias, separate subgroup analyses were carried out between 194 patients at Center 1 and 44 patients at Center 2.

Regarding the subgroup analysis of clinical endpoints among the most common esophageal stricture types, a significant or non-significant superiority of the endoscopic treatment regimen of Center 1 could be observed for patients with peptic strictures (▶ **Table 3**). However, patients with radiogenic strictures were observed to respond clinically better to the lower-frequency endoscopic treatment regimen of Center 2 (▶ **Table 3**).

▶ **Table 3** Subanalysis of endoscopic outcomes matched for the most common causes of esophageal stricture.

Characteristics and outcomes	Post-radiation stricture			Peptic stricture		
	Center 1*	Center 2*	P	Center 1*	Center 2*	P
Patients, n (%)	19 (43.2)	22 (11.3)		70 (36.0)	10 (22.7)	
Predilator size, median (range)	7 (5–8)	6 (5–8)	0.22	8 (5–11)	7 (5–9)	0.14
Maximum dilator, median (range)	16 (10–17)	14 (9–16)	<0.001	15 (12–18)	13 (12–16)	0.003
Difference in dilation diameter, median (range)	9 (3–11)	7 (4–10)	0.008	7 (4–12)	6 (3–9)	0.18
Dilator size of 15 mm was achieved, n (%)	14 (74)	11 (50.0)	0.13	45 (75.0)	4 (57.1)	0.37
Time span until dilator size of 15 mm was achieved (days), median (range)	101 (0–855)	150 (14–750)	0.07	76 (0–1743)	167 (14–410)	0.04
No. of Savary dilations until dilator size of 15 mm was achieved, mean (range)	4 (1–7)	10 (2–28)	0.002	4 (1–21)	9 (3–21)	0.01
Dilator size of 15 mm not achieved, n (%)	5 (26)	11 (50.0)		15 (25.0)	3 (42.8)	
Time span until maximal dilator size was achieved (days), median (range)	155 (0–706)	60 (7–214)	0.13	21 (0–295)	212 (0–648)	0.57
No of Savary dilations until maximal dilator size was achieved, median (range)	3 (1–4)	4 (2–9)	0.45	4 (1–13)	4 (1–7)	0.21

*Center 1: University Hospital Frankfurt; Center 2: Sana Klinikum Offenbach.

Comparing clinical results at both centers among subgroups matched for the localization of esophageal stricture, a better therapeutic response to the treatment regimen at Center 1 could be observed for most of the defined endpoints (▶ **Table 4**). Nevertheless, a higher number of endoscopic treatment episodes required to reach freedom from dysphagia was observed in Cohort 1 among subgroups with an upper and mid-esophageal stricture (▶ **Table 4**).

Analyzing endoscopic endpoints among subgroups with the same localization or the same type of esophageal stenosis, considerably better results could be observed for the endoscopic regimen at Center 1: a significantly larger maximal dilator size and a significant or non-significant trend toward a larger dilation diameter difference could be detected in all subgroups of Cohort 1 (▶ **Table 5**, ▶ **Table 6**). Subanalysis of predilator sizes revealed that a significant difference between both centers could only be observed for proximal esophageal strictures (▶ **Table 5** and ▶ **Table 6**). Among all other subgroups, the cohorts did not differ significantly regarding predilator size.

Discussion

To our knowledge, this is the first study to systematically evaluate the relevance of the time intervals between ED sessions in endoscopic treatment of benign esophageal strictures. Most guidelines recommend repetition of endoscopic bougienage at weekly intervals [4, 11, 14]. However, trials evaluating the best interval between two endoscopic sessions are still lacking and most recommendations are based on published reports and on practical experience [9, 15].

Our study compared the concepts of two different endoscopy centers, which differed in time intervals for bougienages: Center 1 performed bougies at an average time interval of 2 days, whereas Center 2 designed a larger break between two ED sessions and performed bougienages only every 2 to 3 weeks, as in most prepublished articles [3, 5].

The results of our study demonstrate that the higher-frequency treatment regimen at Center 1 seems to be more effective in treating most types of esophageal strictures: a significant superiority of Center 1 could not only be observed for reaching a maximal dilator size of 16 mm after the first three ED sessions, but also for all further endoscopic endpoints, which in turn also correlated with better clinical responses of this cohort. Duration as well as the number of ED sessions required to achieve freedom from dysphagia was shorter and lower in patients of Center 1. Moreover, patients treated with high frequency ED presented symptom-free over a longer period of time until dysphagia recurred. Only the number of therapy episodes required to achieve permanent freedom from dysphagia was significantly lower in patients at Center 2, which could be due to the different therapy concepts of both centers. At Center 1, patients were often scheduled electively at regular intervals of 6 months while endoscopic dilation treatment at Center 2 was only resumed in cases of recurring dysphagia. Thus, a higher number of therapy episodes at Center 1 despite a significantly lower number of ED sessions may be due to different endoscopic therapy concepts and may not necessarily reflect an inferiority of the treatment regimen at Center 1 in this endpoint.

However, when interpreting these results, it must be taken into consideration that the cohorts differed significantly in fre-

▶ **Table 4** Subanalysis of endoscopic outcomes matched for localization of esophageal stricture.

Characteristics and outcomes	Proximal esophageal stricture			Mid-esophageal stricture			Distal esophageal stricture		
	Center 1*	Center 2*	P	Center 1*	Center 2*	P	Center 1*	Center 2*	P
Patients, n (%)	42 (21.6)	27 (61.3)		43 (22.2)	7 (3.6)		77 (39.6)	11 (25.0)	
Predilation diameter, median (range)	8 (5–11)	7 (5–12)	0.002	9 (5–15)	7 (5–9)	0.05	8 (6–9)	9 (5–13)	0.05
Maximum dilator, median (range)	15 (10–18)	14 (9–16)	0.001	16 (11–18)	13 (10–16)	0.001	15 (11–18)	14 (11.16)	0.002
Difference in dilation diameter, median (range)	7 (3–15)	7 (2–11)	0.55	7 (5–9)	7 (3–9)	0.29	7 (3–12)	6 (3–9)	0.52
Dilator size of 15 mm was achieved, n (%)	27 (64.2)	13 (48.1)	0.2	38 (88.4)	4 (57.1)	0.04	38 (19.6)	5 (11.4)	0.002
Time span until dilator size of 15 mm was achieved (days), median (range)	106 (0–1003)	143 (14–750)	0.006	30 (0–195)	573 (18–2107)	0.02	128 (11–4015)	919 (14–4015)	0.004
No. of Savary dilations until dilator size of 15 mm was achieved, median (range)	4 (1–7)	9 (2–28)	0.001	3 (1–10)	7 (6–8)	0.01	3 (1–21)	9 (3–21)	0.002
Dilator size of 15 mm not achieved, n (%)	15 (35.7)	14 (51.9)		5 (11.6)	3 (42.9)		39 (20.1)	6 (13.6)	
Time span until maximal dilator size was achieved (days), median (range)	125 (0–1420)	281 (0–3326)	0.04	4 (0–13)	104 (70–152)	0.03	131 (0–706)	232 (0–648)	0.11
No of Savary dilations until maximal dilator size was achieved, median (range)	4 (1–22)	4 (1–8)	0.5	2 (1–3)	10 (9–12)	0.03	4 (1–10)	5 (1–9)	0.22

*Center 1: University Hospital Frankfurt; Center 2: Sana Klinikum Offenbach.

quency of localizations and in etiologies of esophageal strictures. Patients in Cohort 2 predominantly presented with radiation strictures in the upper third of the esophagus, which are often remarkably fibrotic and resistant. Compared to peptic strictures, radiation strictures are often difficult to treat and have the tendency to be refractory or to recur despite dilatation [3, 13, 16, 17]. In contrast, patients in Cohort 1 primarily suffered from peptic stenosis, which usually represents a simple and short stricture and responds better to esophageal dilatation [12]. In addition, predilator diameter size was significantly larger in patients in Cohort 1, which may also explain significantly larger post-dilation diameters in this cohort, and thus, impede the correct interpretation of endoscopic results.

Thus, a separate subgroup analysis based on different localizations and on most frequent etiologies of esophageal strictures was carried out to rule out heterogeneity of treatment effects. Regarding endoscopic outcomes, the subgroup analyses confirmed what was already observed: a higher frequency of endoscopic sessions, as practiced in Center 1, led to significantly better treatment results in all subgroup analyses, also in patients suffering from a radiation stricture (▶ **Table 5**, ▶ **Table 6**).

Analyzing the dilator diameter difference resulted in considerably larger values for the treatment regimen of Center 1. Since the difference between pre-dilation and post-dilation diameter enables a comparison of both treatment regimen regardless of the predilator size, these results confirm our observations of the higher-frequency treatment regimen being more effective regarding endoscopic endpoints.

Beyond that, clinical outcomes were compared between the referring subgroups. Comparing patients with a mid or lower esophageal stricture as well as patients with a peptic stricture, again a significant or non-significant superiority of the higher-frequency endoscopic treatment regimen at Center 1 could be observed for most of the clinical endpoints. However, the subgroup analysis of patients with a radiation stricture revealed controversial results. Patients treated with the lower-frequency endoscopic regimen at Center 2 achieved a better clinical response in the majority of clinical endpoints. In contrast to other

▶ **Table 5** Subanalysis of clinical outcomes matched for localization of esophageal stricture.

Characteristics and outcomes	Proximal esophageal stricture			Mid-esophageal stricture			Distal esophageal stricture		
	Center 1*	Center 2*	P	Center 1*	Center 2*	P	Center 1*	Center 2*	P
Patients, n (%)	42 (21.6)	27 (61.3)		43 (22.2)	7 (3.6)		77 (39.6)	11 (25.0)	
Time span until freedom from dysphagia was achieved (days), median (range)	97 (0–884)	74 (5–515)	0.33	170 (0–1890)	288 (76–838)	0.99	126 (0–2310)	406 (0–4107)	0.06
No. of ED sessions until freedom from dysphagia was achieved, median (range)	4 (1–36)	6 (1–57)	0.36	4 (1–36)	6 (2–57)	0.65	3 (1–41)	11 (6–46)	<0.0-01
No. of therapy episodes containing Savary dilations until long-term freedom from dysphagia was achieved, median (range)	3 (1–14)	1 (1–9)	0.02	3 (1–4)	1 (1–9)	0.09	2 (1–16)	3 (1–6)	0.71
Time span to recurrence of dysphagia, median (range)	286 (0–1700)	113 (0–1261)	0.72	92 (16–1042)	185 (98–378)	0.14	111 (19–1035)	92 (11–1792)	0.33

ED, esophageal dilation.

▶ **Table 6** Subanalysis of clinical outcomes matched for the most common causes of esophageal stricture.

Characteristics and outcomes	Post-radiation stricture			Peptic stricture		
	Center 1*	Center 2*	P	Center 1*	Center 2*	P
Patients, n (%)	19 (43.2)	22		70 (36.0)	10 (22.7)	
Time until freedom from dysphagia was achieved, median (range)	511 (1–2310)	102 (14–2128)	0.05	194 (0–1890)	202 (8–4107)	0.24
No. of ED sessions until freedom of dysphagia was achieved, median (range)	7 (2–41)	6 (1–57)	0.63	6 (1–34)	18 (9–46)	0.008
No. of therapy episodes containing Savary dilations until long term-freedom of dysphagia was achieved, median (range)	4 (1–16)	1 (1–9)	0.002	4 (1–6)	4 (1–14)	0.55
Time span to recurrence of dysphagia, median (range)	139 (72–566)	91 (14–2128)	0.45	394 (24–1418)	158 (24–507)	0.85

ED, esophageal dilation.

esophageal stenoses, the fibrosis driven by radiation often affects the tissues surrounding the esophagus, creating a non-compliant mediastinum [18, 19, 20, 21]. As a consequence, radiation strictures are frequently refractory to dilatation. The treatment concept at Center 2, which is characterized by longer time intervals between two ED sessions, may represent a better approach to effectively and gradually treat fibrotic and refractory radiogenic strictures. Moreover, the fibrotic nature of radiogenic strictures may also be the reason why post-dilation diameters of more than 14 mm are often not achieved. Thus, endoscopic dilation, which is primarily focused on clinical symptoms and on achieving freedom from dysphagia as practiced at Center 2, may be the better approach to treat those patients. Nevertheless, those contrary results of a better clinical response in patients at Center 2 may also be driven by a relatively small sample size of patients with radiation strictures in both subgroups und should be further evaluated in more representative cohorts.

Beyond conducting subanalyses of different stricture localizations and etiologies, we performed a regression analysis in

▶ **Table 7** Univariate and multivariate analysis of factors associated with achieving a dilator size of 15 mm.

Parameters	Dilator size 15 mm achieved, n = 180	Univariate	Multivariate	
		P value	OR (95% CI)	P value
Gender, n (%)		0.08		
Males	137 (76)			
Females	42 (23)			
Age (years)	71 (20–96)	0.04		
Stricture localization, n (%)		0.28		
Proximal	40 (22)			
Mid	42 (23)			
Distal	71 (39)			
Elongated	4 (2)			
Etiology of stricture, n (%)		0.82		
Peptic	59 (33)			
Post-radiation	25 (14)			
Eosinophilic esophagitis	4 (2)			
Anastomotic stenosis	11 (6)			
Corrosive	1 (0.6)			
Post-therapeutic after ER-/APC-therapy or RFA	58 (32)			
Pseudodiverticulosis	5 (3)			
Desquamative esophagitis	0 (0)			
Papillomatosis	0 (0)			
Other	7 (6)			
Center, n (%)		<0.001	(2.49–76.82)	0.003
1	158 (88)			
2	22 (12)			
Stricture length, n (%)	2 (1–10)	0.22		

order to better analyze the influence of different ED regimens of both centers. With regard to the endoscopic endpoint of reaching a bougie size of 15 mm, age and the different bougienage concepts were observed to be predictors in a univariate analysis. However, in a consecutive multivariate analysis, the different bougienage regimens in the cohorts were the only independent predictor of reaching a bougie size of 15 mm (▶ **Table 7**). Regarding achieving the clinical endpoint of reaching freedom from dysphagia by a low number of ED sessions (≤4), stricture localization as well as the different bougienage concepts of both centers were observed to be predictors in a univariate analysis. However, again in a consecutive multivariate analysis only the bougienage regimens of both centers turned out to be the only independent predictive factors of reaching freedom from dysphagia by a low number of EDs (▶ **Table 8**). Because the two treatment regimens significantly differ in frequency of ED and further bias factors such as the localization or etiology of strictures were taken into account by regression analysis, the results underscore the general superiority of a higher-frequency ED approach. Nevertheless, whether all stricture types and localizations benefit from this approach or whether individual strictures such as radiogenic ones should be dilated by a lower frequency cannot be answered on the basis of this analysis and must be investigated prospectively.

AEs such as hemorrhage or retrosternal pain were observed to be equally frequent in both centers. Concerning the incidence of serious AEs, gastric perforation and bougienage ulcers were observed to be more frequent with the higher-frequency endoscopic regimen. However, no significant difference could be detected between the regimens. Thus, it can be assumed that higher-frequency dilatations are not associated with an increased risk of complications.

▶ **Table 8** Univariate and multivariate analysis of factors associated with low number of Savary dilations (≤4) until freedom from dysphagia is achieved

	Low number of EDs (≤4) until freedom from dysphagia is achieved, n = 98	Univariate	Multivariate	
		P value	OR (95% CI)	P value
Gender, n (%)		0.77		
Male	74 (76)			
Female	23 (23)			
Age (years)	70 (15–94)	0.78		
Stricture localization, n (%)		0.008		0.12
Proximal	19 (19)			
Mid	20 (20)			
Distal	41 (42)			
Elongated	2 (2)			
Etiology of stricture, n (%)		0.13		
Peptic	26 (27)			
Post-radiation	8 (8)			
Eosinophilic esophagitis	4 (4)			
Anastomotic stenosis	6 (6)			
Corrosive	1 (2)			
Post-therapeutic after ER-/APC-therapy or RFA	40 (41)			
Pseudodiverticulosis	1 (2)			
Desquamative esophagitis	1 (2)			
Papillomatosis	0 (0)			
Other	3 (3)			
Center, n (%)		<0.001	1.4 (2.00–9.67)	0.002
1	88 (90)			
2	10 (10)			
Stricture length, n (%)	1 (1–5)	0.22		

A major limitation of our study was its retrospective design. Endoscopic procedures including the number of dilations per session as well as the time interval between two sessions were at physician discretion and not dictated by a predefined study protocol. Moreover, due to the lack of standardized and systematic protocol, detailed assessment of dysphagia by means of a scoring system was also not possible. However, both participating centers complied with the guidelines for endoscopic dilation in clinical practice [5, 11]. Moreover, neither study cohort was randomized. Thus, a certain heterogeneity of both study cohorts concerning the cohort sizes (Cohort 1: 194 patients, Cohort 2: 44 patients) as well as the frequency of localizations and etiologies of esophageal strictures might influence the study results and lead to selection and surveillance bias. Finally, the number of certain stenoses such as anastomotic or post-therapeutic strictures was too small in both sub-cohorts to conduct further subanalyses. Thus, our results refer primarily to radiogenic and peptic stenoses. Based on the overall analysis of both centers, only assumptions can be made for further types of strictures.

Conclusions

In summary, our multicenter, retrospective study demonstrates that endoscopic bougienage is generally more effective for treating non-radiogenic esophageal strictures if the time interval between two ED sessions is kept short. Current guidelines recommend performing endoscopic dilatations once per week. However, our results show that the treatment concept of higher-frequency bougienages every 2 to 3 days, as practiced at Center 1, led to significantly better clinical and endoscopic results in those types of strictures. However, our data

also showed that radiogenic strictures, in contrast, should be treated with low-frequency ED. The clinical response was observed to be significantly better for patients with radiogenic strictures if ED was performed with lower frequency and longer time intervals. Nevertheless, our study is retrospective and our data may not be generalizable to all types of strictures. Thus, prospective studies with representative study cohorts are warranted to further evaluate these results.

Conflict of Interest

The authors declare that they have no conflict of interest.

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