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A retrospective review of risk factors for recalcitrant peptic strictures.

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DECLARATION

I, Babalwa Ndlebe, hereby declare that the work on which this review article is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABBREVIATIONS

1. PS - Peptic Stricture
2. GORD - Gastro-oesophageal reflux disease
3. PPI - Proton pump inhibitor
4. EBD - Endoscopic balloon dilatation
5. TTS - Through the scope
6. NHLS - National health laboratory services
7. HIV - Human immune virus
8. COAD - Chronic obstructive airway disease
9. ECCR - Electronic Continuity of Care Record
10. ARVs - Anti-Retrovirals
11. IQR - Interquartile range
12. EMR – Endoscopic mucosal resection
13. ESD - Endoscopic submucosal dissection
14. RFA - Radiofrequency ablation
15. LOS - Lower Oesophageal sphincter
16. SEMS - Self expanding metal stent

ABSTRACT

Introduction:

Peptic strictures (PS) are a common benign cause of dysphagia, but a scarcity of local data is available as regards identifying risk factors associated with recalcitrancy.

Methods:

Single center retrospective audit of PS undergoing endoscopic management between 1st March 2018 and 1st March 2022, aiming to identify recalcitrancy risk factors.

Results:

Of 69 patients (37 male, 53.4%) with PS, 27 (39.1%) were diagnosed with recalcitrant strictures. Most strictures were positioned distally (53; 76.8%) with an associated hiatus hernia in 52 (75.4%). While comorbidities were not associated with recalcitrancy, younger age was a risk factor (recalcitrant stricture group median age 51 (IQR 38.5-61.0 years) versus non-recalcitrant group median age 62.5 (IQR 48.5-70.8 years); $p=0.044$). Although HIV status did not affect recalcitrancy risk, taking oral antiretrovirals (ARVs) was significantly associated with PS recalcitrancy ($p=0.032$; OR 4.55).

Presenting degree of dysphagia ($p<0.001$; OR 16), requiring more than 3 dilatations ($p<0.001$), and smaller index residual oesophageal lumen ($p<0.001$) were all significantly associated with stricture recalcitrancy. Fourteen patients were temporarily stented (having a total of 24 stents placed). Thirteen patients had post endoscopic complications with most of these complications occurring amongst the recalcitrant group ($n=11$). Four complications occurred during endoscopy, two partial thickness tears managed endoscopically, a gastric perforation requiring an over-the-scope-clip closure and one sedation related hypoxia requiring a short period of bag-mask-valve ventilation and sedation-reversal. Two deaths occurred in the cohort; one from a suspected aspiration pneumonia five days after last dilatation and one from a suspected missed oesophageal perforation (2.3% immediate endoscopic intervention complication rate for 265 dilatations performed).

Conclusion: Locally pill oesophagitis related to ARVs has been identified as a potential cause of recalcitrancy; identifying at-risk patients early may allow for management adjustments to improve outcomes.

PUBLICATION READY MANUSCRIPT

INTRODUCTION

Peptic stricturing is defined as a narrowing of the oesophageal lumen due to uncontrolled gastroesophageal reflux disease (GORD) resulting in chronic inflammation⁽¹⁾. Fibrous tissue deposition and collagen leads to scarring and stricture formation⁽²⁻⁴⁾. Peptic strictures (PS) remain the most common benign oesophageal strictures but have been declining in incidence over the past 20 years due to increasing use of proton pump inhibitors (PPI)^(1, 2). Recalcitrant strictures are either refractory or recurrent strictures. A refractory oesophageal stricture is a stricture in which there is failure to achieve an oesophageal diameter of more than 14mm after 5 sessions of endoscopic dilatations with 2-week intervals^(2, 5-8). A recurrent oesophageal stricture is a stricture in which there is an inability to maintain an oesophageal luminal diameter of more than 14mm for more than 4 weeks after achieving an initial diameter of 14mm^(2, 8). Approximately 90% of benign oesophageal strictures are dilated successfully after 3-5 dilatations without needing further intervention⁽⁸⁻¹⁰⁾. The remaining 10% are recalcitrant strictures, requiring a longer course of treatment, increasing the risk of iatrogenic complications, nutritional deficits and economic burden to the health care system⁽²⁾.

Predictors of recurrence of benign oesophageal strictures include persistent symptoms of dysphagia despite oesophageal dilatation, persistence of heartburn after dilatation despite use of recommended dose of PPI, a narrow index diameter of the stricture (diameter of less than 9mm), female sex, etiology of the stricture and achieving maximum stricture diameter of 13-15mm during the first 3 endoscopic dilatation interventions^(2, 9, 11, 12). Dysphagia to solids only occurs when there is a substantial oesophageal luminal compromise with a residual lumen of 18mm usually remaining asymptomatic⁽¹³⁾. Other

symptoms include odynophagia, food impaction, nutritional deficits and weight loss potentially becoming chronic issues⁽²⁾.

The mainstay investigation for oesophageal strictures remains upper gastrointestinal endoscopy that allows defining the characteristics of the stricture, therapeutic interventions and excluding concurrent pathology^(4, 5, 8, 12, 14). Endoscopy should be augmented with fluoroscopy to better define the anatomy of complex strictures. Formal contrast swallow examination, manometric studies for exclusion of coexisting motility disorders and occasionally, cross-sectional imaging may be required when investigating recalcitrant strictures.

While management is multimodal, adequate continued acid suppressive therapy with PPI is essential, with endoscopic intervention required to achieve and maintain oesophageal luminal patency^(1-3, 9, 11, 13, 15-17). Serial bougienage or balloon dilatations are equally effective^(2, 11, 13, 15, 16). Intralesional steroid injections in conjunction with dilatation and incisional therapy or stricturoplasty are additional options employed on an individualized basis in patients with recalcitrant strictures⁽¹⁾. The placement of temporary fully covered metal stents may occasionally be required^(1, 2, 15).

There remains a paucity of international data on benign oesophageal strictures in general and their risk factors for recalcitrance with a complete absence of data in the South African context. This study aims to audit local peptic oesophageal strictures and attempts to identify factors associated with stricture recalcitrance. The objective of the study is to evaluate if these factors (the patients age, gender, comorbidities, ARV use amongst those who were HIV positive, recreational substance use, initial degree of dysphagia, stricture position, presence of a hiatus hernia, number of dilatations and index stricture diameter) were associated with stricture recalcitrance. Identification of factors associated with stricture recalcitrance will assist with future early identification of patients who are potentially high risk for having recalcitrant strictures. Early identification will facilitate counselling these patients regarding likelihood of prolonged invasive treatment modalities. In addition, this data will assist the unit with

financial planning as treatment duration of the recalcitrant strictures is longer and has financial implications that need to be factored in during budget allocation.

METHODS

Patient population:

This is a single center retrospective study of all adult patients (>18 years) with peptic strictures presenting to the Upper Gastrointestinal Surgery Unit at Groote Schuur Hospital between 1st March 2018 to 1st March 2022 (study approved by the University of Cape Town Human Research Ethics Committee, reference 2021/251). Patients eligible for inclusion into the study were identified from a prospectively maintained registry of all endoscopy procedures performed by the Upper Gastrointestinal Surgery service at Groote Schuur Hospital (registry approved by the University of Cape Town Human Research Ethics Committee, reference number 031/2015). All adult patients that presented to the unit with dysphagia due to benign PS were included in the study. Malignant and benign oesophageal strictures other than PS were excluded. Once stricture recalcitrancy was confirmed, repeat biopsies were routinely taken to exclude missed pathology. At no point during the study were the patients individually contacted for information, consent nor their management altered for the benefit of the study as the study data was retrospectively collected.

Definitions:

A recalcitrant stricture was defined as either refractory or recurrent. Refractory strictures fail to achieve an oesophageal diameter of more than 14mm after 5 sessions of endoscopic dilatations with 2-week intervals^(2, 5-8). A recurrent stricture is where there is an inability to maintain an oesophageal luminal diameter of more than 14mm for more than 4 weeks after achieving an initial diameter of 14mm^(2, 8). Dysphagia was graded using a system previously described by Earlam et al (grade 0: normal swallowing, grade 1 occasional difficulty to swallow solid food, grade 2 occasional difficulty swallowing solids, grade 3: unable to swallow minced foods, grade 4: unable to swallow pureed or liquidized foods and grade 5: unable to swallow liquids or saliva)⁽¹⁹⁾. We further defined significant dysphagia as equal to or more than grade 4 dysphagia. The first bougie dilator that was used to dilate

the stricture was used as the index diameter of the stricture. Index diameter was further defined as being mild, moderate, severe or extremely severe (mild: more than 11mm; moderate: 9-11; severe: 6-8mm; extremely severe; less than 6mm). The oesophagus was divided into proximal, mid and distal oesophagus (proximal: less than 20cm from incisors; mid: 20-30 cm from incisors and distal: more than 30cm from incisors).

Endoscopic dilatation technique

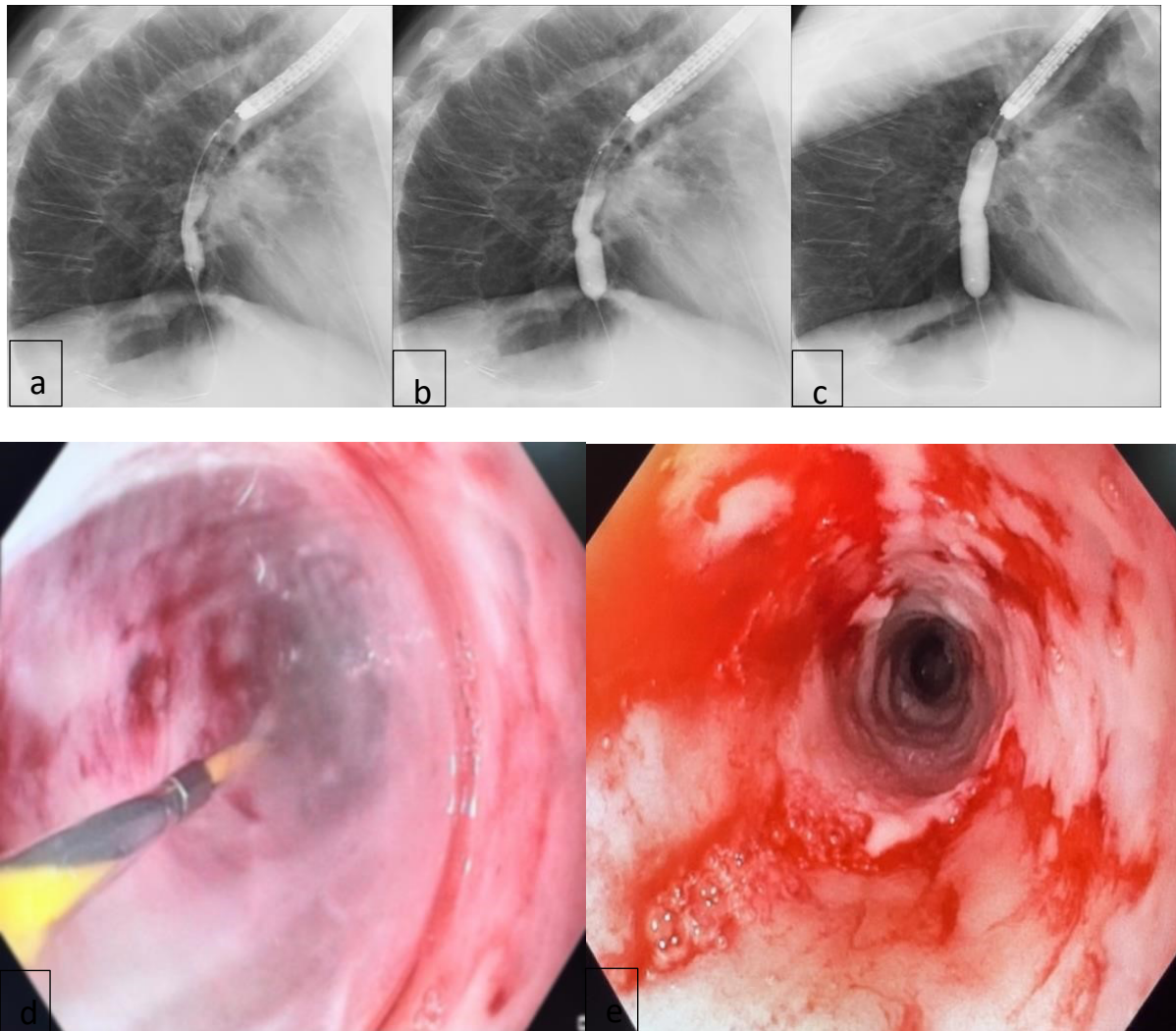
With patients in a left lateral position, an endoscopic dilatation is performed using a standard gastroscope. This is performed simultaneously with fluoroscopy and pharyngeal xylocaine spray plus intravenous conscious sedation with individualized combinations of midazolam, fentanyl or propofol. Nasal prong oxygen and non-invasive blood pressure, pulse and oxygen saturation monitoring are standard. Endoscopic balloon dilatation (EBD), bougienage, incisional therapy, intralesional steroid injection and temporary stenting are available as dilatation treatment modalities in our unit. For PS management, EBD and serial bougienage are the most frequently employed options. The gastroscope is first passed to confirm the presence of the stricture, determine stricture position and if traversable, presence or absence of a hiatus hernia is noted. If the gastroscope passes the stricture before any dilatation, the residual index diameter of the stricture is presumed to be > 11mm. The starting size and type of dilator utilized is at the discretion of the attending endoscopist.

Bougienage is performed over a standard hydrophilic soft-tipped 0.035" guidewire with serial Savary Gillard dilators and gradual incremental size increases (at the endoscopists discretion), with each dilatation performed under fluoroscopic guidance. EBD are performed using over-the-wire, through the-scope (TTS) balloons with a mixture of 50% water to 50% radio-opaque contrast for balloon insufflation using a hydrostatic device with pressures according to manufacturer specifications correlating to specific diameters. TTS balloons are insufflated during continuous fluoroscopy, ideally with the stricture 'waist' positioned mid-balloon. Duration of insufflation is 120 seconds. Figure 1 demonstrates endoscopic balloon dilatation under fluoroscopic guidance and endoscopic view of the stricture dilatation. Bougienage is favored where possible due to cost. On completion of any dilatation, a review

of the dilated area is routinely performed by repeat gastroscopy. If any concern for a full thickness tear exists, contrast is injected into the oesophageal lumen under fluoroscopy to evaluate for any extravasation.

Temporary fully covered self-expanding metal stents (SEMS) are occasionally placed in specific circumstances for PS; either as an immediate management of iatrogenic stricture perforations or when the performance status or nutritional state of the patient precludes safe dilatation of a high-grade stricture. These stents are then removed within 4 - 6 weeks with the patient subsequently joining a scheduled dilatation program. Dilatation intervals are usually between 2 – 4 weeks, with shorter intervals scheduled for severe or extremely severely narrow strictures. Restrictions as regards transport availability from rural areas are factored in. All patients diagnosed with PS are routinely placed on chronic twice daily PPI and asked to modify their risk behaviors. Patients were followed up until complete stricture resolution with no dysphagia or were lost to follow up.

Figure 1: Endoscopic Pneumatic balloon dilatation of distal oesophageal stricture under fluoroscopic guidance.



a. Beginning of dilatation with stricture positioned mid balloon. b. Balloon partially inflated. c. Balloon fully inflated. d. Endoscopic view of distal benign peptic stricture pneumatic balloon dilatation. e. endoscopic view post balloon dilatation

Assessment of outcomes:

The following data categories were collected: patient demographics, co-morbidities, chronic medication, patient reported smoking and substance use, GORD symptoms, prior or present H2 receptor antagonist or PPI use and the degree of dysphagia on initial presentation. Endoscopy findings were

recorded with emphasis on position of stricture, residual lumen, dilatation technique employed, maximum dilatation size achieved, immediate technical success or any procedural complications (as per the Clavien-Dindo classification) ⁽¹⁸⁾.

Subsequent dilatation frequency and interval duration were noted until clinical resolution of dysphagia, achievement of endoscopic success or until the end of the study period.

Statistical analysis:

Data analysis was done using Microsoft Excel and IBM SPSS Statistics (version 29.0.0.0). Patient demographics, peptic stricture details and management were described using simple descriptive statistics, with mean +/- standard deviation for parametric data and median with inter-quartile range for non-parametric data. Univariate analyses were performed to assess for any factors associated with stricture recalcitrance using Chi-squared test for univariate categorical data and Kruskal-Wallis test to allow for comparison of multiple groups with non-parametric data. Single factors (not multiple groups) found to be significant were further analyzed using odd's ratio. A p-value of <0.05 was considered.

statistically significant. The factors that were evaluated for association with recalcitrance included the patients age, gender, comorbidities, ARV use amongst those who were HIV positive, recreational substance use, initial degree of dysphagia, stricture position, presence of a hiatus hernia, number of dilatations and index stricture diameter.

RESULTS

A total of 69 patients (32 female; 37 male) with peptic strictures met the inclusion criteria. The median age was 56. Recalcitrant strictures were diagnosed in 27 (39.1%) while 42 (60.9%) patients had non recalcitrant strictures. Common comorbidities included hypertension, type II diabetes mellitus, dyslipidemia, chronic obstructive airway disease and human immune deficiency virus (HIV). Seven patients (25.9%) with recalcitrant strictures were on antiretroviral (ARV) therapy. Smoking was the most common recreational substance used, followed by alcohol. In the recalcitrant group of patients,

48% (n=13) presented with significant dysphagia at their primary endoscopic dilatation, while in the non-recalcitrant group only 23.8% (n=10) had significant dysphagia.

The majority (n=53; 76.8%) presented with distal oesophageal strictures; 14 had mid-oesophageal strictures and two patients had proximal strictures. A hiatus hernia was diagnosed endoscopically in 52 patients (75.4%). In 22 patients, while the peptic stricture was noted, the residual oesophageal lumen was wide enough to easily allow scope passage and as such no dilatation was required. The remaining 47 all required one or more dilatations (table 2), with patients requiring more than 3 dilatations later all meeting the definition for recalcitrancy (either refractory or recurrent). A total of 265 dilatations were performed in this cohort. Forty patients had bougie dilatations, 4 patients had both EBD and bougie dilatation. Fourteen patients required temporary oesophageal stenting prior to entering the dilatation program. None of the patients were managed with EBD only.

The decision for temporary stenting with a fully covered SEMS was made if the patient had a very poor performance status due to frailty, severe malnutrition or a pin-point residual oesophageal diameter precluding safe dilatation. In total 24 temporary stents were placed in these 14 patients with some patients having multiple stents replaced over time. The majority (n=11, 79%) of stented patients were from the recalcitrant stricture group. Two patients (14%) were managed by stenting only. Eight patients continued with the dilatation program after stent removal; 4 patients were lost to follow up after primary stent placement. Two (14%) patients were dilated with both bougie and EBD following final stent removal, while the remainder by only bougie dilatation (n=10;71%). Six (42%) strictures initially stented subsequently resolved during the study period, while a further 2 (14%) patients were lost to follow-up after having progressed to endoscopic dilatations. Two stented (14%) patients died during the study period (one of severe malnutrition, the second patient of metastatic cervical cancer).

Table 1 demonstrates endoscopic intervention related complications during the study period. A total of 13 patients had complications. There were four immediate complications that occurred during

endoscopy, two partial thickness tears managed endoscopically, a gastric perforation requiring an over the scope-clip closure of a small gastric defect and one sedation-related hypoxia necessitating a short period of bag-mask-valve ventilation and sedation-reversal. Two deaths occurred in the dilatation cohort: one from a suspected aspiration pneumonia five days after last dilatation and one death from a suspected missed oesophageal perforation. This equates to a 2.3% immediate endoscopic intervention complication rate for 265 interventions performed for this cohort. Eleven delayed stent-related complications occurred: nine early stent migrations and two failed removals of stents due to mucosal ingrowth after delayed patient return.

Table 1 : Complications post endoscopic intervention.

Type of stricture	Presence of complications		Clavien -Dindo classification ¹	
	Yes	No	Grading	Number of complications
Recalcitrant	11	16	I	5
			II	1
			III(a)	3
			III(b)	0
			IV(a)	0
			IV	0
			V	2
Non-Recalcitrant	2	40	I	0
			II	0
			III(a)	2
			III(b)	0
			IV(a)	0
			IV(b)	0
			V	0

¹Classification of Surgical complications according to Dindo et al

Table 2 shows association between potential risk factors and recalcitrant peptic strictures. Risk factors for recalcitrant peptic strictures included age (median age 62 vs 51, $p = 0,04$), initial degree of dysphagia ($n=24$ vs 18, odds ratio 16, p value $< 0,001$), number of dilatations ($p=0,001$), index stricture diameter and ARV usage ($p=0.032$; OR 4.55). The patients who had these potential risk factors were likely to receive aggressive treatment strategies over prolonged period compared to those who did not have these potential risk factors. HIV status and smoking were not associated with recalcitrant strictures. Gender, comorbidities, presence of a hiatus hernia and stricture position were not associated with recalcitrant peptic strictures. The non-recalcitrant group of patients were less likely to receive prolonged and aggressive treatments as they presented with lower grades of dysphagia with wider index diameter of the stricture that sometimes did not require intervention when the endoscopist could pass the scope easily prior to intervention.

Table 2: Association between potential risk factors and recalcitrant peptic strictures

		Not recalcitrant			Recalcitrant		p-value	Odd's ratio
Age - median (IQR) years		62,5 (48,5 - 70,8)			51,0 (38,5 - 61,0)		0,044*	
		Total	n	%	n	%		
Gender	Female	32	21	65,6	11	34,4	0,455	
	Male	37	21	56,8	16	43,2		
Comorbidities	None	22	12	54,5	10	45,5	0,465	
	Yes	47	30	63,8	17	36,2		
Hypertension	No	50	27	54,0	23	46,0	0,06	
	Yes	19	15	78,9	4	21,1		
Diabetes	No	63	38	60,3	25	39,7	0,762	
	Yes	6	4	66,7	2	33,3		
Hypercholesterolemia	No	65	40	61,5	25	38,5	0,649	
	Yes	4	2	50,0	2	50,0		
COAD	No	65	40	61,5	25	38,5	0,649	
	Yes	4	2	50,0	2	50,0		
HIV	No	57	37	64,9	20	35,1	0,137	
	Yes	12	5	41,7	7	58,3		
ARVs	No	59	39	66,1	20	33,9	0,032*	4,55 [¶]

	Yes	10	3	30,0	7	70,0		
Substances	No	52	32	61,5	20	38,5	0,843	
	Yes	17	10	58,8	7	41,2		
Smoking	No	55	34	61,8	21	38,2	0,751	
	Yes	14	8	57,1	6	42,9		
Recreational Drug Use	No	68	41	60,3	27	39,7	0,423	
	Yes	1	1	100,0	0	0,0		
Alcohol	No	65	40	61,5	25	38,5	0,649	
	Yes	4	2	50,0	2	50,0		
Initial Dysphagia Degree	At least soft diet	26	24	92,3	2	7,7	<0,001*	16 [¶]
	Liquids only	42	18	42,9	24	57,1		
Stricture Position	Proximal <20cm	2	1	50,0	1	50,0	0,497	
	Mid 20-30cm	14	10	71,4	4	28,6		
	Distal >30cm	53	31	58,5	22	41,5		
Hiatus Hernia	No	14	10	71,4	4	28,6	0,354	
	Yes	52	30	57,7	22	42,3		
No. of Dilatations	0 Dilatations	25	23	92,0	2	8,0	<0,001*	
	1-2 Dilatations	20	15	75,0	5	25,0		
	3-5 Dilatations	12	4	33,3	8	66,7		
	>5 Dilatations	12	0	0,0	12	100,0		
Index Stricture Diameter	<6mm	3	1	33,3	2	66,7	<0,001*	
	6-8mm	21	8	38,1	13	61,9		
	9-11mm	13	6	46,2	7	53,8		
	>11mm	32	27	84,4	5	15,6		

Abbreviations IQR= Interquartile range; HIV = Human immune virus; COAD=Chronic obstructive airway disease; LDL= Lower than detectable limit; ARVs= Antiretrovirals

*p Value $\leq 0,05$ [¶]Odds ratio ≥ 1

Discussion

Approximately 90% of benign oesophageal strictures are dilated successfully after 3-5 dilatations without needing further intervention while the remaining 10% are recalcitrant strictures, requiring a longer course of treatment⁽⁸⁻¹⁰⁾. While peptic strictures generally respond well to endoscopic dilatation, 39% of our benign peptic strictures were diagnosed recalcitrant, which is much higher than the 10%

generally reported⁽⁸⁻¹⁰⁾. The aim of this study was to determine if any local risk factors exist for the development of recalcitrancy specifically in peptic strictures.

Previous literature has demonstrated multiple risk factors associated with recalcitrant strictures, these include persistent symptoms of dysphagia despite oesophageal dilatation, persistence of heartburn after dilatation despite use of recommended dose of PPI, a narrow index diameter of the residual oesophageal lumen (diameter of less than 9mm), female sex, etiology of the stricture and only a maximum stricture diameter of 13-15mm achieved after the first 3 endoscopic dilatations^(2, 9, 11, 12). Similar to previous reports, this study demonstrated a significant association between stricture recalcitrancy and narrow index diameter, specifically less than 6mm ($p < 0,001$), significant initial grade of dysphagia and number of oesophageal dilatations required. In addition, younger age was associated with recalcitrant peptic strictures in our study.

While 68% of the cohort were taking chronic medications for various co-morbidities, the use of ARVs specifically was demonstrated to be a potential cause of recalcitrant strictures ($p = 0,032$; OR 4.55). This association is most likely due to pill oesophagitis. The most common mechanism of pill induced oesophageal mucosal injury is due to local acid or hyperosmolar mucosal burn resulting from pills being retained in the oesophagus⁽²⁰⁾. Medication that has previously been described to cause pill oesophagitis by this mechanism, includes ascorbic acid, ferrous sulphate, potassium containing tablets and antibiotics such as doxycycline, tetracyclines and clindamycin. Non-steroidal anti-inflammatory drugs, aspirin, bisphosphonates and chemotherapy agents such as paclitaxel have also been described to cause local mucosal burn⁽²⁰⁾. Pill oesophagitis may also be caused by medication that causes LOS relaxation, thus perpetuating the effect of acid reflux, such as nitroglycerines, anticholinergics, beta adrenergic agonists, aminophyllines and benzodiazepines⁽²⁰⁾. There is some evidence demonstrating a higher risk of Barrett's oesophagus and oesophageal adenocarcinoma secondary to this type of pill oesophagitis⁽²⁰⁾. Patients with peptic strictures are always encouraged to crush their tablets and advised to ingest the crushed tablet with copious amounts of fluid to help prevent pill oesophagitis. Interestingly, HIV positive status

including high viral load did not demonstrate an association with recalcitrancy of the stricture, rather it appears to be the actual risk of pill oesophagitis from the ingestion of ARVs. Figure 2 below demonstrates treatment algorithm of benign oesophageal strictures⁽²¹⁾. The corner stone in management of peptic strictures PPIs and endoscopic dilatation with either a bougie dilatator or EBD, with no differences in safety and efficacy between the 2 types of dilation techniques^(1-3, 9, 11, 13, 15-17, 21, 22). Previous literature has demonstrated an 80-90% clinical success rate amongst patients that are managed with these modalities. Our local success rates for the endoscopic treatment of PS are considerably lower at 60.8%. The minority of patients that remain symptomatic despite these treatment modalities require prolonged periods of dilatation due to chronic inflammation and fibrosis that cannot be easily mediated with expansile, transient radial and longitudinal forces applied during dilatation⁽¹⁰⁾. These patients require early identification and, risk stratification, with counselling regarding possible treatment duration and potential intervention complications.

Endoscopic dilatation with intralesional steroid injection using triamcinolone acetate is an alternative combination therapy for recalcitrant benign peptic strictures^(21, 22). Intralesional steroid injection is thought to inhibit inflammatory response in order to reduce stricture formation, collagen synthesis, fibrosis and chronic scarring⁽²²⁾. Steroid injection has been shown to reduce the number of required dilatations and increase the dysphagia free period⁽²²⁾. Triamcinolone acetate is unavailable in South African state practice and our unit has had little success with alternative forms of available injectable steroids. Mytomycin C is an antineoplastic agent that has been used as an alternative or to supplement intralesional steroid injections, with positive outcomes reported predominantly in pediatric benign oesophageal strictures. Mytomycin C inhibits fibroblast proliferation and collagen synthesis^(21, 22). No definitive evidence presently exists for the use of Mitomycin C in adult recalcitrant oesophageal

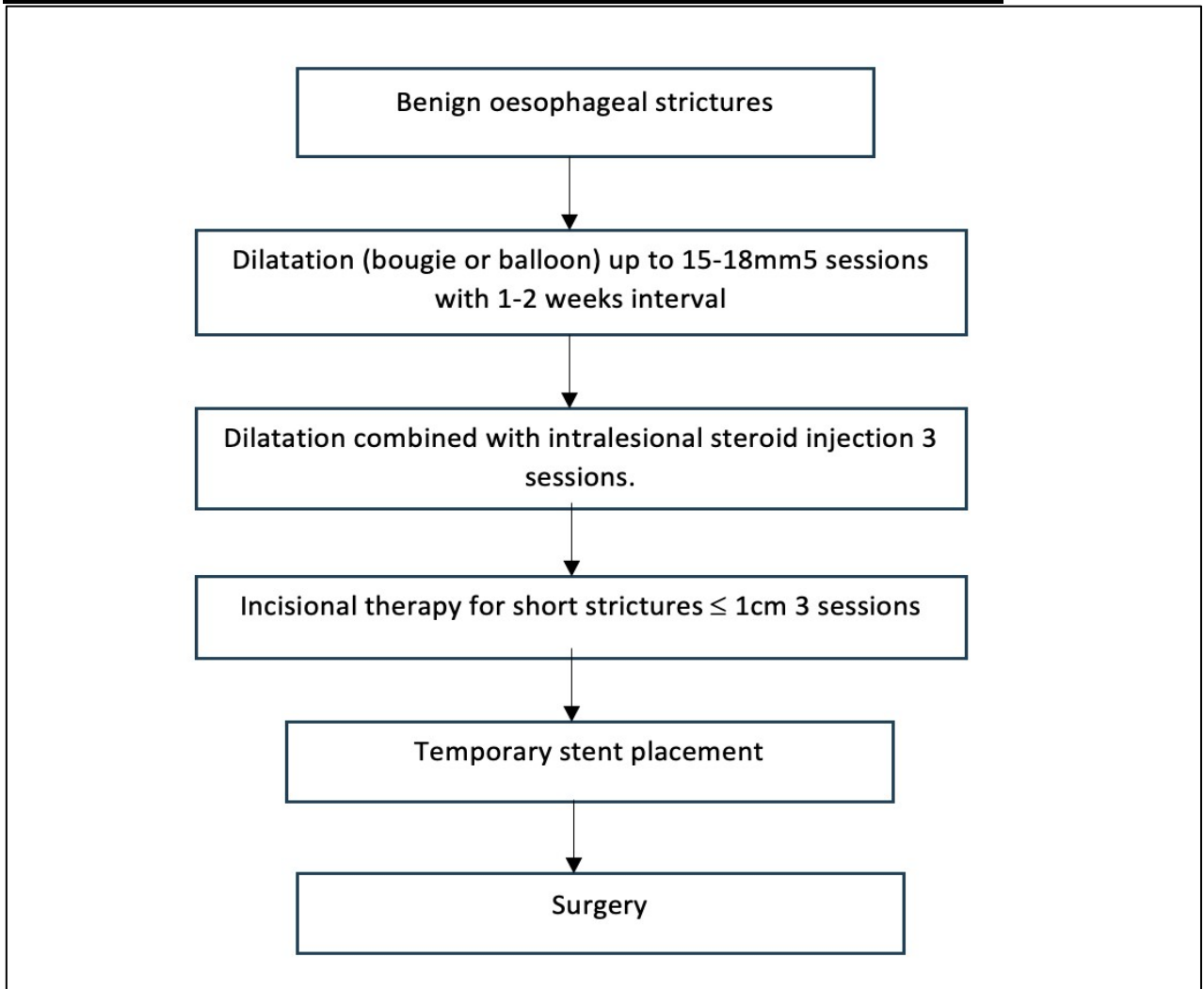
strictures.

Incisional therapy is a further alternative treatment option recommended for short, simple strictures^(21, 22). A maximum of 3 sessions of incisional therapy are recommended, after which alternatives should be considered if strictures persist⁽²²⁾. Short, fibrotic strictures as often seen with anastomotic strictures,

lend themselves well to incisional therapy. However, in our experience the active inflammation usually present in peptic strictures, does not readily avail itself to safe incisional therapy. While daily self-dilatation is reported as a successful alternative in refractory strictures⁽²³⁾, our institution only has one full set of bougie dilators and thus cannot accommodate sending patients home with these. A further divergence from international treatment algorithms (figure 2) in our local management of recalcitrant strictures is the timing of serial dilatations; due to the far distances rural patients are required to travel, timing of dilatation does not always overlap well with international guidelines as regards interval frequency.

Oesophageal stenting is a safe alternative modality for the management of benign peptic strictures, usually recommended towards the end of an algorithm for the treatment of persistent strictures. Using SEMS is thought to increase the overall dilatation period of the stricture when compared to other dilatation alternatives, there is however no data to support this^(21, 22). SEMS are thought to reduce the rate of restricturing, by remodeling of the stricture while the stent is in place maintaining luminal patency⁽²²⁾. The stent is kept in for 6-8 weeks but should not exceed 12 weeks to reduce the risk of mucosal ingrowth related to a hyperplastic tissue reaction⁽²²⁾. In our unit, oesophageal stenting was used as an alternative or in conjunction with bougie and sometimes balloon dilatation. When the index diameter of the stricture was deemed too narrow to allow for safe dilatation in a patient severely malnourished or frail, primary stenting was offered to avoid potential complications of stricture dilatation by bougie or EBD. Stenting was also offered as treatment progression following failed endoscopic dilatation in recalcitrant strictures. There was a 42% stricture resolution rate amongst the patients who were managed with oesophageal stents in this study thus making stenting a safe alternative bridging tool when other modalities of dilatation are not safe to perform. The literature demonstrates 35 - 45% clinical resolution rate amongst stented patients⁽²²⁾. Evidence shows that use of stenting reduces the number of dilatations and increases the dysphagia free periods⁽²²⁾. Care must be taken though when stenting distal benign strictures, these tend to migrate in our experience and are often associated with worsening volume reflux when crossing the LOS.

Figure 2: Treatment algorithm for patients with benign oesophageal strictures*



* Treatment algorithm for patients with benign oesophageal strictures according to Fugazza et al⁽²¹⁾

The strength of this study is that there is no local data published previously regarding factors associated with recalcitrant peptic strictures or the management thereof. Limitations are the retrospective nature of the study; it is a single institution review and that local restrictions have forced deviations from internationally recommended treatment algorithms for recalcitrant benign strictures.

CONCLUSION

In conclusion, recalcitrant peptic strictures continue to be an ongoing cause of morbidity locally with lower success rates despite availability of most internationally recommended endoscopic treatment modalities. Younger age, presenting degree of dysphagia, requiring more than 3 dilatations, smaller index stricture diameter and use of oral ARVs were all significantly associated with stricture recalcitrancy. Locally pill oesophagitis related to ARVs has been identified as a potential cause of recalcitrancy. Identifying at-risk patients early will allow management modification to improve outcomes including planning of extensive counselling regarding possibility of prolonged invasive treatment modalities. Early extensive counselling helps psychological preparation of the prolonged treatment and thus help with patient 's insight towards their condition and therefore adherence to treatment plan follow-up. In addition, this data will assist the unit with financial planning as treatment duration of the recalcitrant strictures is longer and may occasionally be associated complications, thus these financial implications would have to be factored in during budget allocation. Future research could investigate the role of surveillance upper gastrointestinal endoscopies in patients who have combination of GORD and these risk factors. Future studies could also investigate whether specific regimens of ARVs are associated with recalcitrant strictures.

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Appendices

Appendix 1: Department of Surgery Research Committee Approval letter



UNIVERSITY OF CAPE TOWN



Department of Surgery
Departmental Research Committee
A/Prof Maritz Laubscher
Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 5108
Email: maritz.laubscher@uct.ac.za

8 Sep 2021

Dr B Ndlebe

Department of Surgery
University of Cape Town

Dear Dr Ndlebe

RE: Project 2021/251

PROJECT TITLE: A Retrospective Review Of Risk Factors For Recalcitrant Peptic Strictures

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

Yours sincerely

Signed by candidate

A/PROF MARITZ LAUBSCHER
CHAIR SURGICAL DRC

Appendix 2: Human Research Ethics Committee approval.



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

20 October 2020

HREC REF: 641/2020

Dr Galya Chinnery
E23 Upper GIT Surgery
Main Building, GSH
Anzlo Road
Observatory
7925
Email: galya.chinnery@uct.ac.za
Student email: eybmoy001@myuct.ac.za

Dear Dr Chinnery

PROJECT TITLE: A RETROSPECTIVE REVIEW OF BENIGN OESOPHAGEAL STRICTURE MANAGEMENT AT GROOTE SCHUUR HOSPITAL- U/G CANDIDATE-MISS MOYA EYBERS-SUB-STUDY LINKED TO R031/2015

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 and 06 July 2020, found on the following website link:
<http://www.health.uct.ac.za/fhs/research/humanethics/about>

Approval is granted for one year until the 30 October 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Ms Moya Eybers will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate Institutional approval, where necessary, before the research may occur.

HREC 355/2020 le

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 355/2020 le

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As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
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- Where available, URLs for the references have been provided.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
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- I/We agree to pay the Article Publishing Charges as per the Authors' Guidelines.

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Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

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- (iv) exact contribution of each author must be stated.

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All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

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The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

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Original articles on research relevant to surgery should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words. Five keywords should be included.

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Short reports should not exceed 1 500 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings,

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Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version. Five keywords should be included.

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Video case reports should not exceed 1 500 words with 10 references and 6 figures. Heading should include Summary (not exceeding 100 words) and Case description (with three subheadings: Introduction, Case presentation and Discussion). The video file format must be only MP4 or MOV and should not exceed 300 MB and 8 minutes. Video case reports will be published online only. The summary and the URL will appear in the printed version. Five keywords should be included.

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How to do it submissions should address a practical aspect of surgical or interventional (endoscopic or radiological) patient management in which a best practice technique or method to advance optimal patient management is presented in a standardised format. The submission should be structured with a short contextual introduction focussing on the indications for the procedure, followed by numbered sequential points that explain and illustrate the procedure and its complications. The total word count should not exceed 1500 words with a maximum of 10 references and 6 figures. Five keywords should be included.

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Opinions, etc. should not exceed 1 000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

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Review articles relevant to surgery should not exceed 5 000 words, with a maximum of 50 references and no more than 6 tables or figures. A summary of 250 words or less is required. Five keywords should be included.

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Letters to the editor should be 400 words or less with only one image or table.

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Obituaries should be 900 words or less and should be accompanied by a photograph.

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This section accepts static images displaying conditions that surgeons experience in clinical practice. It is important to note that this article type is not intended as a vehicle for case reports.

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2. Submitted as perfect focus high resolution images that clearly demonstrate the abnormality.
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5. Include a title for the submission comprising up to eight (8) words.
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 2. **A teaching point that makes clear the clinical importance of the submission.**

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