A Review of the Incidence and Management of Complications following Malignant Oesophageal Stenting

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DECLARATION

I, Gilbert Teyangesikayi, hereby declare that the work on which this dissertation/thesis 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. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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LIST OFT ABLES AND FIGURES

ABBREVIATIONS

HREC	Human Research Ethics Committee
SEMS	Self-expanding Metal Stent
ICU	Intensive care unit
NHLS	National Health Laboratory Service
SCC	Squamous cell carcinoma
AC	Adenocarcinoma
HIV	Human Immunodeficiency Virus
OGJ	Oesophagogastric junction
PEG	Percutaneous endoscopic gastrostomy
NSAIDs	Non-steroidal anti-inflammatory drugs
CT	Computed tomography
TNM	Tumour Node Metastasis
LMIC	Lower and middle-income countries
IQR	Interquartile range

Abstract

Background

Stenting provides effective palliation of malignant dysphagia for irresectable tumours due to either local invasion, metastatic disease, or poor performance status. Immediate technical success rates are very high, with clinical improvement approaching 90% in most reported series. Complications specific to oesophageal stenting include perforation, pain, aspiration, volume reflux, bleeding, migration, tumour overgrowth and ingrowth.

Methods

This retrospective audit of palliative oesophageal stenting over a three-year period (March 2018 - March 2021), with review of technical and clinical outcomes, aimed to determine local incidence and management of complications.

Results

The majority (73.4%) of palliative stents were placed for squamous cell carcinoma (SCC) with a total of 354 stent insertion attempts undertaken in 297 patients (49 requiring multiple stents). Three unsuccessful insertions and six incorrectly placed stents, all immediately addressed, equated to an immediate technical success rate of 97.5%. Most (346; 98.6%) were fully covered stents; only two partially covered and three uncovered stents were inserted. Seventeen stents (4.8%) were placed for a confirmed trachea-oesophageal fistula. Twenty-one (6.0%) immediate insertion-related complications occurred, including two oesophageal perforations. Five patients required removal of proximal stents on the same day due to significant globus sensation or chest pain. There was no mortality due to immediate stent insertion related complications. Dysphagia improvement was registered in all (100% clinical success rate) successful stent insertions.

Late complications occurred in 73 (20.8%). The most frequent indication requiring reintervention was tumour overgrowth (30; 10.1%) occurring at a median 63.5 days (IQR 41.0 - 103.3 days). Stent migration occurred in 18 patients (6.1%) at a median 28.0 days (IQR 10.0 - 52.8 days). Of the total 354 placed stents, 264 (75.2%) had no documented complications for the lifetime of that stent. When comparing the rate of stent migration and tumour overgrowth by tumour position, distal tumours (>30cm from the incisors) were 8.93 times ($p<0.0001$) more likely to migrate than proximal tumours (<30cm). Tumour overgrowth was more likely in proximal tumours, but this did not reach statistical significance.

Conclusion

Oesophageal stenting is an effective and safe palliation of malignant dysphagia. Outcomes reported by this cohort from a low/middle income setting compare favorably to high volume international units.

PUBLICATION READY MANUSCRIPT

A REVIEW OF THE INCIDENCE AND MANAGEMENT OF COMPLICATIONS FOLLOWING MALIGNANT OESOPHAGEAL STENTING

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Key words

Malignant dysphagia; Self-expanding metal stents; palliative oesophageal stenting; oesophageal stenting outcomes; technical success; clinical success

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3260

Introduction

Oesophageal carcinoma is the eighth most common cancer and the sixth most frequent cause of cancer-related death worldwide with developing nations making up more than 80% of total cases and deaths, *Napier et al* [1]. According to *Jemal et al [*2] and *Torre et al [*3], the highest incidence rates are found in Asia and Sub-Saharan Africa, and South Africa is amongst the countries with the highest incidence rates globally. Most patients, over 50%, with oesophageal cancer present late with advanced, incurable, or inoperable disease. In South Africa well over 90% of patients with squamous cell oesophageal cancer present with high grade dysphagia (greater than 2 on the *Pinkus and Mellow scale* [8]) at primary presentation, *Loots et al* [4].

While the mainstay of curative therapy remains surgery with perioperative chemoradiotherapy, stenting provides palliation of malignant dysphagia in oesophageal or proximal gastric cancer in those not candidates for surgical resection due to extensive local or metastatic disease or poor performance status [5,6,7]. Indications for stenting are increasingly expanding to include benign conditions such as corrosive and peptic strictures, anastomotic strictures, perforations, anastomotic leaks, tracheoesophageal fistulae, and refractory oesophageal variceal bleeding [6, 9].

The use of stenting has been shown to provide an effective method of palliation for malignant dysphagia. Most published series have shown overall immediate technical success rate in up to 100%, with clinical success (improvement in dysphagia score) approaching 90%. The resumption of oral intake enhances quality of life as well as the nutritional status of the patient [5, 6, 7].

However, while there has been significant improvement in the outcomes of upper gastrointestinal stenting associated with advances in the design of the stents from the rigid plastic endoprostheses of the early 90s to the current self-expanding metallic, plastic as well as biodegradable forms, stenting is still attendant with numerous and significant complications [6]. Complications of stent placement can be classified as early or delayed (late). Early complications occur immediately or within 2-4 weeks after stent placement and include foreign body sensation, pain, gastroesophageal reflux, migration, bleeding, and perforation. Late complications are more common than early ones and are defined as complications that occur at least 2-4 weeks after stent placement, including migration, tumour ingrowth and overgrowth, proximal peptic strictures, and aero-oesophageal fistula [6]. Notably, early complications are

decreasing because of recent advances in SEMS and delivery systems, but delayed complications still occur in up to 65% patients, with a re-intervention rate as high as 50% [5, 6]. Among both early and delayed complications, migration is the most common complication, occurring at a rate of 7%-75% depending on the type and design of stent [5, 6].

The Groote Schuur Hospital Upper Gastrointestinal Unit is referred significant numbers of advanced upper gastrointestinal cancers from a wide referral catchment. We aim to document local complications associated with our palliative malignant stent placements.

Methods

Study design & data source

This was a single center retrospective review of patients presenting to a tertiary hospital endoscopy unit with malignant dysphagia requiring palliative stent placement. This study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 218/2021). Data was extracted from the Upper Gastrointestinal Surgery Registry (HREC R031/2015).

Patients

All patients presenting to Groote Schuur Hospital with clinical features of dysphagia and requiring palliative endoscopic oesophageal stenting between 1 March 2018 and 31 March 2021 were evaluated for potential inclusion. Patients with confirmed irresectable malignant strictures of the oesophagus were included in the study. Histological confirmation of malignancy was required prior to referral for stenting, with results accessed online via the National Health Laboratory Service (NHLS). Irresectability was determined by the presence of metastatic disease or unresectable invasion of adjacent structures as determined by cross-sectional imaging using computerised tomography (CT). Tumour position was documented in centimeters from the incisors, with distal stents defined as those placed for tumours below 30cm from the incisors. In addition, a locally obstructing oesophageal tumour and/or a patient with a poor performance status of over 2 according to the Eastern Cooperative Oncology Group [24], usually precludes any curative surgical intervention. Such patients clinically amenable to endoscopic stenting only, were also included into the study cohort. Stents placed for benign indications or malignant gastric outlet obstructions were excluded. Dysphagia was graded according to the dysphagia grading system originally proposed by Mellow and Pinkus [8]:

- 0 = normal/no dysphagia
- 1 = ability to eat some solid food
- 2 = ability to eat semisolids only
- 3 = ability to swallow liquids only
- 4 = complete dysphagia (inability to swallow saliva)

Outcomes

The primary objective of this study was to determine the technical and clinical outcomes of palliative endoscopic stenting of malignant oesophageal dysphagia in our endoscopy unit. It aimed to determine the incidence of early and late complications associated with stent placement and their subsequent management, as well as the technical and clinical success rates, comparing with other international high volume endoscopy units. Furthermore, this study aimed to determine if there are any differences between low and/or middle income (LMIC) and first world countries as regards patient demographics and pathology of irresectable malignant dysphagia in those presenting for palliative endoscopic stenting.

Statistical analysis

Data exploration and analysis was done using Microsoft Excel and patient demographics, histology, technical success, and complication rates were described using simple descriptive statistics. Parametric data were described using mean with standard deviation and non-parametric data were described using median with inter-quartile range.

Results

Patient demography

Over the three-year study period (March 2018 - March 2021) a total of 297 patients required 354 (49 requiring multiple) oesophageal stent insertion attempts for malignant disease. Of these patients 143 (48.14%) were males with a mean age of 61.0 (+/- 12.4) years, range 31 - 94 years. Female patients were slightly older with a mean age of 64.7 (+/- 11.9) years, range 29 - 90 years. A total of 129 patients (43.43%) had no known medical comorbidities, while the remaining 168 patients had a total of 247 separate comorbidities (table **1).** A total of 133 patients (44.8%) admitted to using illicit substances. On initial presentation, 282 patients (94.9%) had advanced dysphagia, only tolerating liquids or less. Of these a total of 35 patients (11.8%) had complete dysphagia and were unable to even swallow their own saliva.

Pathology

The majority required palliative stenting for irresectable squamous cell carcinoma (73.4%), with adenocarcinoma responsible for 21.2% of malignant obstructing strictures. Most adenocarcinoma tumours were situated distally with 57 of 63 (90.5%) tumours starting at 30cm or more from the incisors. In eight patients, the primary oesophageal malignancy was neither SCC nor adenocarcinoma, and included four undifferentiated carcinomas, three oesophageal neuroendocrine carcinomas, and one oesophageal melanoma. A further eight patients were obstructed due to extrinsic malignant compression and included primary lung cancer (four), metastatic lymph node disease from cervical pathology (two) and one breast one cancer (table 2). When comparing demographics of the patients with adenocarcinoma (n=63) versus those with SCC (n = 218), it is evident that the average ages were equal in the two groups (62.6 +/- 12.2 years for adenocarcinoma and 62.9 +/- 12.2 years for SCC), but that SCC patients were more likely to be female compared to those with adenocarcinoma (57.8% female vs 31.7%, respectively).

Stent Insertions

A total of 354 stent insertion attempts were undertaken over the study period with only three unsuccessful insertions and six incorrectly placed stents, which were all immediately addressed, equating to an immediate technical insertion success rate of 97,5%. Technical success was defined as inserting a stent across the obstructing stricture correctly under endoscopic and fluoroscopic guidance with no repositioning required, with flow of contrast demonstrated through the stent into the distal lumen beyond the stricture. Of the total 351 inserted stents (including those six that were initially incorrectly placed), 346 (98.6%) were fully covered stents, with only two partially covered stents and three uncovered stents inserted. Seventeen stents (4.8%) were placed for a confirmed trachea-oesophageal fistula. Most patients (248 patients, 83.50%) required only one stent (table 3). Distally placed stents (163 stents; 46%) accounted for almost half of the cohort.

Complications

Twenty-one (6.0%) immediate insertion-related complications occurred (table 4), including two oesophageal perforations. Five patients required removal of the stent on the same day as

they did not tolerate the stent due to high placement with globus sensation or significant associated chest pain. Two perforations caused by the primary stent insertion (and not a concomitant oesophageal dilatation) occurred both just below the cricopharyngeus and therefore could not be stented.

In the first patient a very proximal malignant stenting was required. The proximal flange of the stent opened above the cricopharyngeus and was immediately removed. The patient was chronically ill with a poor performance status and was admitted on IV antibiotics, and subsequently had an oesophageal dilatation with percutaneous endoscopic gastrostomy (PEG) placement prior to discharge. The second proximal perforation was managed with distal oesophageal stricture stenting, nasogastric tube placement, IV antibiotics and subsequent discharge home. Relief of dysphagia was registered in all successful stent insertions allowing for oral intake at the time of discharge, including patients managed for acute stent-related complications. There was no mortality due to immediate stent insertion-related complications (table 4).

Late complications occurred in 73 cases (20.8%) (table 5). The most frequent reason for representation requiring reintervention was tumour overgrowth (30; 10.1%) and stent migration (18; 6.1%). Repeat intervention for tumour overgrowth occurred at a median 63.5 days (IQR 41.0 - 103.3 days) post primary stenting. Stent migration occurred in a total of 18 patients at a median 28.0 days OQR10.0-52.8 days.

Of the total 351 placed stents, 264 (75.2%) had no documented complications requiring endoscopic reintervention that we are aware of. While all patients stented across the oesophagogastric junction are routinely discharged on a combination of proton pump inhibitors and antacids, severe symptomatic clinical complaints of volume reflux remained a significant problem in 12 patients prompting repeat endoscopy. No antireflux stents were inserted in this cohort.

Table 1. Patient demographics and clinical characteristics in 297 patients undergoing endoscopic stenting for oesophageal malignant stricture palliation.

Demography	Number n %
Gender	
Male	143 (48.1)
Females	154 (51.9)
Co-morbidities	
Hypertension	102 (34.3)
HIV Positive	30(10.1)
Chronic Lung Disease	25 (8.4)
Diabetes Mellitus	23 (7.7)
Known malignancy (other than the obstructing malignancy)	14 (4.7)
Tuberculosis	14 (4.7)
Neurological	10 (3.4)
Cardiac	9 (3.0)
Hypercholesterolemia	8 (2.7)
Other	12(4.0)

Table 2. Pathological conditions underlying the dysphagia requiring palliative stenting in the 297 patients.

Type of Malignancy (n = 297)	Number (% of cohort
Squamous Cell Carcinoma	218 (73.4)
Adenocarcinoma	63 (21.2)
Lung Cancer (extrinsic)	5 (1.6)
Undifferentiated/Poorly Differentiated Carcinoma	4 (1.3)
Oesophageal Neuroendocrine Carcinoma	3(1.0
Other	
Cervical carcinoma	2 (0.7)
Oesophageal melanoma	1 (0.3)
Breast carcinoma	1 (0.3)

Table 3. Number of stents required per patient

Number of Stents Per Patient (n = 297)	% Of cohort
1 Stent	248 (83.5
2 Stents	42 (14.1)
3 Stents	6 (2.0)
4 Stents	1 (0.3)
Total stents placed	354

Table 4. Early stent related complications

Immediate Insertion-related Complications n = 21	Number % of cohort
Incorrect stent placement (immediately addressed*)	6 (2.0)

Sedation-related complication (requiring reversal of sedation)	6 (2.0)
Stent not tolerated (requiring removal on the same day)	5 (1.6)
Oesophageal perforation	2 (0.7)
Bleeding	1 (0.3)
Aspiration	1 (0.3)
Death	0 (0)

* Immediately addressed: 2 x stent repositioned, 2 x stent removed and replaced, 2 x additional stent placed

Table 5. Late stent related complications

Late Stent-related Comp lications n = 73	Number % of cohort
Tumour overgrowth	30(10.1)
Stent migration	18(6.1)
Volume reflux - severe, symptomatic requiring repeat Endoscopy	12 (4.0)
Peptic stricture formation above stent	3 (1.0)
Food bolus obstruction	3 (1.0)
Distal obstruction due to stent lying just above OGJ - requiring Repositioning	4 (1.3)
Other	
Severe stent pain (necessitating removal)	1 (0.3)
Severe globus sensation	1 (0.3)
Narrowing proximal and distal to the stent (due to unknown cause	1 (0.3)

Table 6. Position of stricture (top of tumour in centimeters from incisors)

<20CM	18 5.1%
20-25CM	120(33.9%)
25 - 30CM	96(27.1%)
30-35CM	58(16.4%)
35-40CM	52(14.7%)
>40CM	10(2.8%)

Table 7. Stent migration or tumour overgrowth by site of tumour

	proximal <30cm	distal (>30cm)	odds ratio	p-value
Stent migration	4/234(1.7%)	16/119(13.45)	8.93	<0.0001
Tumour overgrowth	20/234(8.5)	5/119(4.2%)	2.13	0.1324

When comparing the rate of stent migration and tumour overgrowth by site of tumour, it is evident that stented distal tumours (tumour position >30cm from incisors) were 8.93 times more likely to migrate than stented proximal tumours (tumour position </=30cm from incisors), which was statistically significant ($p < 0.0001$). Tumour overgrowth was more likely in proximally stented tumours, but this did not reach statistical significance.

Discussion

This large retrospective study describes the outcomes of palliative oesophageal stent insertions for inoperable malignancy in a single level one hospital endoscopy unit, over a period of three years. Most patients present very late with dysphagia, some with malignant fistulae, and others with malignancy-related haemorrhage. Self-expanding metal stents have become the first-choice palliative intervention in our setting owing to easy access with rapid relief of symptoms [4, 7]. Our technical success rate of 98.6% compares well with both international and other African data (95 - 100%) [5, 6, 7, 11, 12]. It is our preference to insert all oesophageal stents endoscopically under fluoroscopic guidance. All successfully stented patients had significant relief of dysphagia, and/or control of tracheoesophageal fistulae allowing for oral feeds at time of discharge.

While early complications are decreasing because of recent advances in SEMS and delivery systems, delayed complications still occur in up to 65% patients, with a re-intervention rate as high as 50% [5, 6]. In most series, among both early and delayed complications, migration is the most common complication occurring at a rate of 7%-75% depending on the type and design of stent [5, 6, 7, 8, 10, 13]. Our series has shown a similar trend with 6% immediate insertion-related complications, while late complications occurred in 20.8%. Tumour overgrowth was the most common complication and occurred more frequently than migration at 10.1% compared to 6.1% respectively.

While our outcomes compare well with those reported internationally [10, 11, 12, 13, 14, 15, 16, 17], there is a notable variation in these outcomes. Selinger *et al* report on a series of 137 patients from England with an oesophageal adenocarcinoma (AC) incidence of 57.0%, which is notably higher than ours (21.2%) [20]. This is the general trend where Western countries tend to have higher AC rates compared to African and Asian nations. This group's reported outcomes correlate well with our results in technical and clinical success rates; their tumour overgrowth was 10.2% compared to our 10.1%, while their overall complication rate was 41.6% compared to our 29.3%. We suspect our overall complication rates to be lower due to our more frequent proximal stenting patterns with less subsequent stent migrations. A relatively lower migration rate in our series compared to the international literature is likely explained by comparatively fewer distal cancers in our series.

In addition, we have also confirmed a local regional difference in clinical presentation within South Africa regarding the two dominant oesophageal pathologies. While an AC rate of 5.6 - 6.7% was reported by Loots *et al* from KwaZulu Natal [4, 23], resulting in a SCC to AC ratio of 13:1 to 15.9:1, our ratio in this cohort is significantly different at 3.5:1. We suspect divergent population group proportions present in the various South African provinces with different risk profiles to play a role as regards presenting pathology. Govender *et al.,* also from KwaZulu Natal, report a stent migration rate of only 2.2% based on a cohort of 506 stents placed from 2007 to 2011 [7]. By comparison, our stent migration rates (6.1%) are more than double and we postulate that this is in part related to the differences in local pathology position. As distally placed stents are confirmed significantly more likely to migrate in our cohort, and the AC incidence in this cohort is 21.2% compared to the 5.6 - 6.7% reported in KwaZulu Natal [17], we expect our cohort to have a higher stent migration rate. Our distal stent positioning significantly affecting migration rates concurs with previous reports, where fully covered stents, benign conditions and distal location are variables independently associated with migration [23].

Volume reflux is one of the major complications related to oesophageal stent placement and contributes significantly to re-intervention rates. This is mainly related to distal oesophageal and oesophago-gastric junction stent positioning. There are suggestions, supported by a few small studies, that anti-reflux stent designs improve volume reflux symptoms, but there has not been sufficient evidence to support this. In a systematic review and meta-analysis of randomized controlled trials, Pandit *et al.* recently found a trend towards reduced dysphagia with anti-reflux stents compared with standard stents, but no statistical difference with regards to volume reflux [21]. In our series, 12 out of 297 patients (4.0%) reported significant clinical regurgitation of volume reflux that required re-intervention. This rate is high considering that only approximately 20% of our patients had distal malignant strictures. We did not deploy any anti-reflux stents in our cohort due to unavailability thereof during the study period. These results may suggest a need for further research into more efficacious anti-reflux designs coupled with larger multicentre prospective randomized studies.

Ferndale et al. from KwaZulu Natal in South Africa [18] report a 90% palliation rate due to late presentation, which correlates with our experiences in Cape Town. Similarly, our high palliation rates are because of most patients presenting to our unit with advanced disease,

associated high dysphagia grades, or metastatic disease frequently coupled with a very poor performance status [24] related to delayed presentation.

Limitations in this study include lack of accurate survival data due to poor follow-up, as most patients come from referral centers and return post-stenting for palliation at their base hospitals. Many come from rural areas with limited access to transport and subsequent specialist follow-up. Secondly, not all patients are formally staged by CT prior to presentation for palliative stenting. If performance status is such that any further oncological or surgical treatment is precluded, stenting is performed on clinical assessment. This is to improve the patient's immediate quality of life and an attempt to spare cross-sectional imaging, locally a very limited available resource, for those who may potentially benefit from subsequent further treatment options. Furthermore, patients presenting with complete obstruction are stented primarily and subsequently offered imaging only after review at a multidisciplinary meeting two weeks later if their performance status has improved post-stenting. As such, we are unable to report on accurate TNM staging in this cohort.

Conclusion

Oesophageal stenting has proven to be a very effective, easily accessible, and safe method for treating palliative malignant dysphagia. Technical success, complications, and clinical outcomes in this cohort from a tertiary hospital endoscopy unit in a low/middle income country compare well to other high resource international centres.

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Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMM

HREC 219/2020sa

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature: Delegate		Date	4/7/22

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf file to: hrec-enquiries@uct.ac.za

HUMAN RESEARCH ETHICS COMMITTEE
14 JUN 2022
HEALTH SCIENCES FACULTY

Date (when submitting this form)	6 June 2022
HREC REF Number	219/2020
Project Title	A Retrospective review of the incidence and management of early and late complications following upper gastrointestinal stenting
Protocol number (if applicable)	
Principal Investigator	[illegible]
	E23-22 Link Main Building GSH

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
Regrettably we omitted to timeously renew our HREC approval in 2021 for this audit linked to our registry (221/2015 which is approved to Aug 2022). This deviation in protocol occurred due to an error on our part, we completely forgot to renew this substudy.

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, action to address, inform participants.
As this is a retrospective audit of an HREC approved registry (valid consequences to participants.
3.2 Please describe what action(s) have or will be taken to prevent
We have now made an automated reminder on an electronic calendar again.

4. Principal Investigator's acknowledgement of responsibility

Page 1 of 2

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

This signature indicates that PI has reviewed the deviation, [redacted] follow-up action and implemented or plans to implement preventative steps where possible.		
Signed by candidate		6 June 2022