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DISEASES OF THE ESOPHAGUS

Original article

Superiority of anti-reflux stent compared with conventional stents in the palliative management of patients with cancer of the lower esophagus and esophago-gastric junction: results of a randomized clinical trial

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SUMMARY. **Palliation of inoperable esophageal cancer with covered stents aims to relieve progressive dysphagia and improve health-related quality of life (HRQoL). Introducing a stent across the esophagogastric junction in lower third tumors may predispose to unchecked gastro-esophageal reflux (GER). Esophageal stents incorporating an anti-reflux valve have been introduced to address this problem. We prospectively compared an anti-reflux stent with a standard stent in the palliation of inoperable lower third esophageal tumors. Forty-nine consecutive patients with malignant dysphagia were randomized to receive a standard ($n = 25$, group 1) or an anti-reflux stent ($n = 24$, group 2). HRQoL was assessed before stenting, at 1 week and at 2 months, utilizing European Organization for Research and Treatment of Cancer questionnaires QLQ-C30, QLQ-OES24 and reflux questionnaires. Esophageal pH testing was performed within 1 week of the stent insertion. Detailed statistical analysis was employed to assess general QoL, symptoms and pH scores in both groups. Both groups reported significantly improved QoL, health and dysphagia scores at 1 week and 2 months after stenting. Group 2 patients reported significantly ($P < 0.05$) better DeMeester symptom, general reflux scores, and normal pH profile at 1 week. At 2 months DeMeester symptom scores were significantly ($P < 0.05$) better in group 2 compared with group 1. Standard and anti-reflux stents afford comparable relief from dysphagia and improved quality of life in patients with inoperable lower third esophageal cancer. Anti-reflux stents, however, controlled symptomatic and physiologically relevant reflux and should therefore be considered as optimal palliation in this cohort.**

KEY WORDS: **dysphagia, esophageal cancer, gastro-esophageal reflux, stent.**

INTRODUCTION

The incidence of cancer of the lower third of the esophagus and esophago-gastric junction has increased markedly in the developed world over the last 20 years.[1] It is frequently a late diagnosis with local or systemic metastases precluding curative resection. More than 60% of patients present with inoperable disease, and for most patients palliation is thus the treatment goal.[2] The efficacy of self-expanding metallic stents (SEMS) in the palliation of dysphagia, the most debilitating and relentless symptom of the disease, is widely accepted and evidence-based.[3,4] Stenting lower third tumors, however, necessarily involves placing the prosthesis across the esophagogastric junction. This renders the lower esophageal sphincter redundant and permits the unrestricted access of acidic gastric contents to the esophageal lumen, and as many as 95% of patients treated with a standard SEMS may experience gastro-esophageal reflux (GER).[5]

There is therefore a rationale and perhaps a real clinical value to a stent which palliates dysphagia but also prevents reflux, and as such anti-reflux stents are currently undergoing clinical evaluation. Early non-randomized studies suggested that these stents are effective at both relieving dysphagia and controlling reflux.[6–9] Homs *et al.*,[10] however, recently published the results of the first randomized controlled trial evaluating an anti-reflux stent, and reported no difference in GER symptoms or pH measurements when comparing the FerX-Ella Anti-Reflux (Ella-CS, Hradel Kralove, Czech Republic) stent with a standard stent by the same manufacturers. The only evidence therefore, arising from a randomized study is at

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variance with non-randomized evaluation and highlights the requirement for further trials.

The aim of this randomized trial was to compare a new anti-reflux stent (Hanarostent, MI Tech, Seoul, Korea) with a standard stent that has been exclusively employed in this unit for over 10 years.[11] The modified stent contains a membrane at the distal end that functions as a valve.[9] All aspects of patients' clinical, physiological and quality of life measurements were incorporated in the study. The primary endpoints of the study were, (i) relief of dysphagia; (ii) control of symptomatic GER; and (iii) impact on the pH profile of the esophagus post-intervention.

MATERIALS AND METHODS

Patients and design

Over a 24-month period 49 consecutive patients with a lower third esophageal or junctional tumor were recruited. All the patients were judged to require stents that would extend into the stomach. The patients were aware of being randomized. Patients suitable for radiation therapy or chemoradiotherapy as primary treatment were excluded. The patients were blinded as to the type of stent they received (Hanarostent with an anti-reflux valve or a standard Boston Scientific Microinvasive Ultraflex covered stent, Boston Scientific Microinvasive, Natick, MA, USA). Exclusion criteria were excessive tumor length (requiring two stents), esophago-bronchial fistula, prior stent placement and a physical or mental function deemed insufficient for inclusion in a randomized trial. Randomization was by the closed envelope technique and primarily pertained to a cohort size of 40 patients. The study was approved by the hospital Ethics Committee.

Intervention

Stent placement was performed in one hospital either by, or under the supervision of, an experienced endoscopist familiar with both stent types. The Hanarostent stent has an anti-migration design to prevent migration against peristaltic motion.[11] The stents were introduced in the standard fashion under general anesthesia with the patient in the lateral decubitus position. A radio-opaque marker was employed to identify the proximal end of the stricture and radiological guidance was then used to ensure accurate stent deployment. The stent position was subsequently checked endoscopically.

Assessment of stent performance

A research nurse who assessed the patients' health-related quality of life (HRQoL) and follow-up was blinded as to the allocation of patients to each group. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire tool was used to assess quality of life (QoL) and general health-related issues.[12] We used the EORTC QLQ-OES24 instrument to assess certain symptoms which pertain primarily to esophageal cancer patients.[13] The patients were required to fill out these forms prior to stent placement and at 1 week and 2 months post-intervention. GER was further assessed using a reflux scale modified from the DeMeester symptom score.[14] This specific questionnaire was completed only at 1 week and 2 months post-stenting, as it is assumed that an obstructing tumor effectively prevents reflux prior to stent placement across the esophagogastric junction.

Ambulatory pH testing was undertaken within the first week at approximately 4 days post-stenting. Patients had discontinued proton pump inhibitors (PPI) for 10 days and antacids for 48 h before pH monitoring. An antimony pH catheter (Medtronic, Copenhagen) was placed 5 cm below the manometrically determined distal border of the upper oesophageal sphincter. This was connected to a Mark III Digitrapper (Medtronic, Copenhagen) and recorded for a minimum of 20 h. Standard parameters were recorded, including the total percentage of time pH < 4, upright and supine percentages, total number of episodes and DeMeester acid score. Following this procedure all patients were allowed to have antacids and PPI as clinically required; however, no detailed record of use of these medications was recorded in prospective follow up.

Statistical analysis

Power studies performed in other studies indicate that a sample size of 20 patients (10 in each group) is necessary to find statistically significant differences when comparing standard and anti-reflux stents.[10] The efficacy in palliating dysphagia from baseline to 1 week and at 2 months post-intervention were analyzed using a repeated measures analysis (Generalized Wilcoxon-Mann–Whitney rank-sum test) that adjusted for pre-intervention levels. The comparison between the groups in control of gastroesophageal reflux disease symptoms was compared at 1 week and 2 months using a Mann–Whitney rank sum test that adjusted for multiple testing. For pH data, non-parametric data were analyzed using Fisher's exact test for 2×2 contingency tables, and the Wilcoxon rank signed test. Statistical significance was ascribed to a P-value of < 0.05.

RESULTS

Basic demographics and clinical characteristics

Forty-nine consecutive patients (26 men/23 women) with a mean age of 74.7 years (range 40–92) were

Table 1 Demographics and clinical characteristics of the study cohort

	Standard stent (n = 25)	Anti-reflux stent (n = 24)
Age (yrs) (range)	73.9 (61–91)	68.4 (47–86)
Gender (M/F)	17/8	14/10
Mean tumour length (cm) (range)	6.8 (3–12)	6.6 (2–11)
Tumor location		
Distal esophagus (%)	17 (68)	17 (71)
Gastric cardia (%)	8 (34)	7 (29)
Tumor histological type		
Adenocarcinoma (%)	14 (41)	17 (50)
Squamous cell carcinoma (%)	10 (53)	7 (50)
Non-small cell carcinoma (%)	1 (6)	0 (0)

randomized. This represented 74% of patients during this time who were suitable for enrollment. All the patients had advanced disease. Before SEMS placement one patient had received chemo-radiotherapy (standard stent) and another had received radiotherapy (anti-reflux stent). Of the total cohort 25 were randomized to receive a standard stent and 24 to receive the anti-reflux stent. The two patient groups and their basic demographics are outlined in Table 1.

Procedural outcome and complications

All the stents were placed successfully and without any immediate complications. There were two cases of intra-procedural migration in the anti-reflux stent group which were dealt with simply by traction on the 'rescue loop' located at the proximal end of the stent. At a median follow-up of 10 months there was no case of fistula formation or major hemorrhage. There were three cases of severe pain related to stent placement, which affected two patients in the anti-reflux group and one in the standard stent group. All these patients required regular narcotic analgesia and frequent consultation with the pain management team while they were in-patients. There was one case of food bolus obstruction of a standard stent after discharge, which was managed endoscopically.

Questionnaire completion and patient follow-up

All the patients returned questionnaires prior to stenting and at 1 week post-intervention. Eleven (37.6%) patients failed to return questionnaires at 2 months, due to their death or a health-related disability. Twenty-one patients agreed to undergo ambulatory pH testing; however, only 18 (63%) completed the test. All esophageal cancer patients are regularly reviewed by the surgical, oncology and radiotherapy teams with frequent interviews by a dedicated esophageal cancer nurse. Patients were followed through to death, but the last data entry point relating to their symptoms and HRQoL in this study was at 2 months post stent insertion.

EORTC QLQ-C30 and QLQ-OES24 assessment

The EORTC QLQ-C30 and QLQ-OES24 are validated instruments which incorporate a multitude of questions used to assess QoL in cancer patients. Total scores for both tools were linearly transformed such that scales ranged from 0 to 100, with higher scores representing higher levels of symptoms. The questionnaires could thus be totalled in order to calculate a cumulative score. Cumulative scores were calculated for each questionnaire completed and analyzed for statistical significance between specific symptoms pre- and post-stenting (1 week and 2 months). The most pertinent findings of both questionnaires are contained in Table 2, which records changes from the baseline. With regard to the EORTC QLQ-C30, both stents performed equally well at 1 week, as indicated by the significant improvement in patients' HRQoL and their perception of their health status. Similar findings were noted with the QLQ-OES24 cumulative score and patients' ability to swallow solid and soft food. At 2 months both stents maintained a statistically significant benefit, compared to pre-stent scores. This was similarly evident with the QLQ-OES24 cumulative score and ability to swallow solid food. At 2 months the standard stent afforded better passage of soft food. Patients did not

Table 2 Changes from baseline levels at 1 week and 2 months post-intervention

	1 week		2 months	
	Standard stent	Anti-reflux stent	Standard stent	Anti-reflux stent
QLQ-C30	< 0.001	< 0.003	0.003	0.003
QoL	< 0.001	< 0.001	0.001	0.001
Health (solid diet)	< 0.001	< 0.001	0.002	0.003
QLQ-OES24	< 0.001	0.003	< 0.001	0.001
Solid diet	< 0.001	0.003	0.001	0.004
Soft	< 0.001	< 0.001	< 0.005	NS
Liquid	NS	0.004	NS	NS
Swallow saliva	0.002	NS	NS	NS

QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire; QLQ-OES24, European Organization for Research and Treatment of Cancer QLQ-OES24 questionnaire; QoL, Quality of Life.

Table 3 Specific reflux symptom categories in which the anti-reflux stent demonstrated superiority over the standard stent

	1 week post-stent	2 months post-stent
Modified DeMeester score	0.004	0.002
Supine GER symptoms	0.003	NS
Upright GER symptoms	0.02 (NS)	NS
Heartburn severity	< 0.001	0.008

however, perceive any benefit accruing from either stent with regard to the passage of liquid and saliva at 2 months.

Reflux symptoms

The anti-reflux stent performed significantly better, when compared to the standard stent, in preventing GER symptoms. The statistical comparison of standard and anti-reflux stent is shown in Table 3. At 1 week anti-reflux stent patients reported fewer GER and heartburn symptoms both in general and with regard to its positional status. At 2 months this effect was less marked, but the modified DeMeester symptom score remained significantly less in the anti-reflux stent group.

Ambulatory 24 h pH monitoring

Of the 21 patients who agreed to undergo pH monitoring, 18 (63%) completed the test. Ten of these had standard stents and the remaining eight patients were treated with anti-reflux stents. The anti-reflux stent was superior to the standard stent in preventing physiological reflux, as evidenced by the results outlined in Table 4. The acid reflux score was significantly lower in the anti-reflux stent group. The percentage of total recording time, time in the upright position and time in the supine position during which oesophageal pH was < 4 was significantly lower in the anti-reflux stent group. The DeMeester score was abnormal in 60% of patients treated with the standard stent, whereas there were no abnormal DeMeester scores in the anti-reflux stent group.

DISCUSSION

Reflux arising from stenting across the cardia can cause significant discomfort and represents a frequent adverse outcome when using standard SEMS. Debilitating consequences arising from a palliative procedure are undesirable and anti-reflux stents have been designed to address this issue. This study demonstrates the superiority of an anti-reflux stent over a standard stent in alleviating symptoms of GER whilst simultaneously providing comparable relief from dysphagia and equivalent QoL benefits in patients with inoperable esophageal cancer.

This outcome is consistent with other prospective studies. The Dua-Z Anti-Reflux (Boston Scientific, St Albans, UK) stent was compared with a standard Flamingo Microinvasive stent (Wilson Lewis Medical, Letchworth, UK) in a prospective study performed by Laasch *et al.*,[5] who reported similar efficacy in palliating dysphagia and an enhanced ability in preventing reflux with the anti-reflux stent. Ninety six percent of patients in the standard stent group experienced GER, with 76% requiring additional treatment with proton pump inhibitors or pro-peristaltic agents, compared with only 12% experiencing symptoms in the anti-reflux group, and 4% requiring acid suppression. This latter study, however, was not randomized, nor did it encompass 24-h pH monitoring or QoL indices.

In contrast, the only randomized trial to date, by Homs *et al.*,[10] comparing the FerX-Ella anti-reflux stent (Ella-CS, Hradel Kralove, Czech Republic) with a standard stent in a cohort of 30 patients, did not show that the anti-reflux stent prevented symptomatic reflux. In this study, only 36% of patients underwent pH studies, and the EORTC QLQ-OES24 questionnaire was applied only on the day of stenting and once more at 2 weeks post-intervention. Although multiple tests were performed, no correction for this was attempted in their statistical analysis. The authors acknowledge that the inability of the FerX-Ella stent to prevent reflux may in part relate to its design, in particular the valve characteristics (the length, thickness and material of the membrane) and its propensity to migrate, which occurred with 25% of stents in this study. In the conduction of this trial, however, we were able to complete pH studies at an early time point in 63% of the total cohort and significant differences in the esophageal acid exposure time between both groups could be identified. This is consistent with an anti-reflux stent feasibility study performed by Osugi *et al.*[15] comprising relatively few, non-randomized patients ($n = 12$), reporting a significantly higher rate of pH monitor-detected

Table 4 Results of ambulatory pH testing in both stent groups

	DeMeester Score	Total (% of time)	Upright (% of time)	Supine (% of time)	Events
Standard stent	27.6 (0.7–71)	6 (0–18)	1.5 (0.1–21)	4.5 (0–27)	46 (4–147)
Anti-reflux stent	2.1 (0.5–6)	0.3 (1–1.5)	0.5 (0–1.5)	0.3 (0–1.3)	11.5 (1–38)
P-value	0.002	0.004	0.042	0.002	0.006

reflux in their standard stent group (37.8% of the time). This effect also correlates with results from animal model studies evaluating anti-reflux stents.[9] From a statistical perspective, moreover, the methodology in this current study appropriately adjusted for multiple statistical testing.

The results demonstrate that the anti-reflux Hanarostent is superior to the standard Microinvasive stent in that it both controls dysphagia and prevents reflux. If pH and QoL data are extrapolated and compared with the negative study of the FerX-Ella stent, it is reasonable to suggest that the difference may relate to certain properties of the Hanarostent. Unlike the polyurethane and polyethylene valves of other anti-reflux stents, the Hanarostent has a malleable silicone-based membrane that is more sensitive to intra-abdominal pressure, thereby enhancing its ability to remain inverted. It also has a 70 mm long valve, significantly longer than the 47 mm valve found in the FerX-Ella anti-reflux stent. Of note in our study was that no evidence of stent migration was observed: a traditional problem with stents traversing the esophago-gastric junction.

Although this trial demonstrated the superiority of the anti-reflux stent in preventing GER, these effects were better evident at 1 week, compared to 2 months. We cannot explain this pattern at this time. It is possible, but only a speculation, that the physical characteristics of the anti-reflux membrane are lost over time, or that persistent exposure of the valve to acidic material may ultimately affect its dynamics. Further longer term studies are therefore required. In addition, the difficulty with soft foods observed in the study group merits note and further investigation.

In conclusion, the Hanarostent affords clinically relevant respite both from malignant dysphagia and from the reflux associated with stenting the esophago-gastric junction. This is the first randomized trial to support the findings of most feasibility studies performed to date. The attainment of reflux control in addition to the primary goal of relief of dysphagia by the anti-reflux stent suggests that these designs merit careful consideration in this clinical scenario, and we would encourage their evaluation in large randomized studies.

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