

# Trial of self-expandable metallic stents in the palliation of tracheo-oesophageal fistula in carcinoma of the oesophagus

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## Summary

**Subjects.** Fifty-eight patients with cancer of the oesophagus were studied from July 2002 to November 2005. Thirty-seven patients presented with strictures and 21 presented with tracheo-oesophageal fistula (TOF).

**Methods.** There were 35 males and 23 females. Mean age was 57 years. Stents were positioned under fluoroscopic guidance, in the majority of cases under conscious sedation. A contrast study was done on day 1 to assess stent expansion and sealing of the TOF. Data were analysed using Stata Statistical Software, Release 8.0. Survival was calculated using Kaplan-Meier methodology and log-rank tests were used to assess differences. A  $p$ -value  $< 0.05$  was considered to be statistically significant.

**Results.** Stenting was successful in 57 of the 58 patients; 1 perforation occurred at the time of insertion. In total, 68 stents were inserted in 58 patients. Re-stenting was necessary in 10 patients, because of tumour overgrowth ( $N = 5$ ), stent migration ( $N = 3$ ) and recurrent fistula ( $N = 2$ ). Dysphagia improved from a mean score of 2.98 to 1.08. All lesions were squamous cell carcinoma. The positions of the fistulas were proximal ( $N = 4$ ), middle ( $N = 14$ ) and distal ( $N = 3$ ). Over half of the patients in the TOF group had concomitant pneumonia at presentation with decreased survival ( $p = 0.010$ ) and a hazard ratio of 10.86. Two patients died, on days 4 and 7 respectively. Median survival was 91 days (range 0 - 273 days) for the stricture group and 62 days (range 3 - 413 days) for the TOF group, but these differences were not significant ( $p = 0.945$ ).

**Conclusion.** Covered self-expandable metallic stents provide an acceptable option for the palliation of TOF due to cancer of the oesophagus.

Worldwide, cancer of the oesophagus is the 7th leading cause of death, with a 5-year survival of 5%.<sup>1,2</sup> Patients usually present late,<sup>3</sup> are rarely curable and have a very poor prognosis.<sup>2</sup> They are malnourished and dehydrated, with poor respiratory function, especially in those with a tracheo-oesophageal fistula (TOF), and are seldom suitable for extensive palliative intervention.<sup>4</sup> Therapy is therefore aimed at alleviating the dysphagia, improving quality of life, decreasing morbidity and postponing death.

The ideal palliative therapy would have a short procedure time, minimal postoperative discomfort, improvement of the dysphagia and a reasonable survival. Numerous options have been tried.<sup>2,4-9</sup> All have varying degrees of success, with no clear advantages.

Very few patients are suitable for palliative bypass surgery.<sup>3,6,8-11</sup> Radiotherapy worsens TOF. Plastic stents such as the Celestin and the Proctor-Livingstone require general anaesthesia for insertion. As these patients are poor anaesthetic candidates these stents are now seldom used; indeed, patients survive less than 2 weeks in some cases.<sup>10</sup> Clearly, another approach is required.

Self-expandable metal stents (SEMS) provide an alternative. They offer the advantage of insertion under conscious sedation, require a lumen of only 12 mm for positioning and deployment, and mould to the course of the stricture, re-stenting through the lumen is possible, and in the case of TOF the fistula can be completely sealed with a covered stent. We prospectively evaluated the use of SEMS in malignant strictures and fistulas due to carcinoma of the oesophagus.

## Subjects

From July 2002 to November 2005, 21 patients presented with malignant TOF. We then randomly chose 37 patients with malignant strictures, with data complete for the same period, in order to compare survival. There were 35 men and

23 women (male/female ratio 1:0.7). Mean age was 57 years (range 39 - 89 years).

Dysphagia was scored using a standard dysphagia score<sup>7,12</sup> (0 = able to eat most solid foods, 1 = able to eat some solid foods, 2 = able to eat semi-solid foods, 3 = able to swallow liquids only, 4 = complete dysphagia). After radiological assessment, the diagnosis was confirmed by means of biopsy; all the lesions were squamous. In both the stricture and the fistula groups, the majority of patients had involvement of the middle third of the oesophagus (Table I).

Two patients in the TOF group had received prior therapy. The first developed a fistula 2 months after commencing chemo-radiotherapy and the second a month after commencing brachytherapy. Two other patients refused any therapy when initially diagnosed; they subsequently presented with TOF 4 and 5 months later, respectively.

## Methods

The stent used was the Ultraflex oesophageal stent system (Microinvasive, Boston Scientific Corporation, Boston, MA).<sup>4,7,13-16</sup> It is constructed from a knitted Nitinol mesh and is available in two forms, namely covered and uncovered. We used covered stents to palliate TOFs and uncovered stents for strictures. Stents were positioned under general anaesthesia in the first 4 patients and under conscious sedation in the following 54, all under fluoroscopic guidance. Afterwards, the patients were sent to the ward, kept nil per mouth and observed like any postoperative patient. A contrast study was done on day 1 after stenting. If positioning was adequate the patient was started on a liquid diet and then proceeded to a soft diet. The patients were usually discharged on day 2 on at least a soft diet.

Data were analysed using the Kaplan-Meier method. Survival was calculated from the date of stent insertion to the last date of follow-up or death (through next of kin if the patient died at home). The log-rank test was used to compare survival between the two groups. The Cox proportional hazards model was used to compare survival, with covariates such as sex, position of fistula, pneumonia and age. Data were analysed using Stata Statistical Software, Release 8.0. A *p*-value < 0.05 was regarded as significant.

## Results

### Patients with oesophageal carcinoma without TOF

Pneumonia was present in 3/37 patients before stenting, but they responded well to antibiotics and physiotherapy and this did not affect survival. Stenting was successful in 36/37. One patient was perforated at the time of insertion (Table II). Because of his poor overall condition we treated him conservatively and he died within 8 hours of the procedure. This was our only significant immediate complication in this group.

In the remaining patients the dysphagia score improved from a mean of 2.67 to 1.02. The only significant long-term complication was tumour overgrowth, occurring in 3/36 cases. All these patients were re-stented successfully. Median survival was 91 days (0 - 273 days).

### Patients with tracheo-oesophageal fistula

Sealing of the fistula was successful in all 21 patients. However, in 2 patients there were procedural complications (Table II). One patient sustained an iatrogenic sinus at the time of insertion that was detected on the contrast study the next morning. The patient was treated conservatively (kept nil per mouth and given intravenous antibiotics); sealing of the sinus was noted on repeat contrast study on day 7. The patient was subsequently discharged. The second patient had malposition, which was missed on the post-stent contrast study. He then presented 18 days later with severe aspiration pneumonia. A contrast study demonstrated that the proximal end of the stent was situated in the hypopharynx. Unfortunately this patient died shortly after admission.

Pneumonia was very prevalent in the TOF group, with 11/21 patients being afflicted compared with only 3/37 in the stricture-only group. Pneumonia was confirmed radiologically and treated with physiotherapy and intravenous antibiotics.

Long-term complications occurred in 7/21 patients, including stent migration (*N* = 3), tumour overgrowth (*N* = 2) and recurrent fistula (*N* = 2). All were successfully re-stented. Dysphagia score improved from a mean of 3.28 to 1.14; median survival was 62 days (3 - 413 days).

TABLE I. PATIENT CHARACTERISTICS

|                         | Cancer of oesophagus with TOF ( <i>N</i> = 21, 36%) | Cancer of oesophagus without TOF ( <i>N</i> = 37, 64%) |
|-------------------------|---|--|
| <b>Sex</b>              |   |  |
| Male                    | 12 (57%)  | 23 (63%)   |
| Female                  | 9 (43%)   | 14 (37%)   |
| <b>Age (yrs)</b>        | 57.7  | 57.3   |
| <b>Dysphagia</b>        |   |  |
| Pre                     | 3.28  | 2.98   |
| Post                    | 1.14  | 1.08   |
| <b>Pneumonia</b>        | 11/21 (52%) ( <i>p</i> = 0.010)                     | 3/37 (8%) ( <i>p</i> = 0.000)                          |
| <b>Tumour histology</b> | Squamous cell carcinoma (100%)                      | Squamous cell carcinoma (100%)                         |
| <b>Fistula</b>          |   |  |
| Proximal                | 4 (19%)   | 13 (35%)   |
| Middle                  | 14 (67%)  | 21 (57%)   |
| Distal                  | 3 (14%)   | 3 (8%)   |

TABLE II. COMPARISON OF COMPLICATIONS BETWEEN THE TWO GROUPS

|                        | Cancer of oesophagus with TOF (N) | Cancer of oesophagus with TOF (N) |
|------------------------|-----------------------------------|-----------------------------------|
| Iatrogenic perforation | -                                 | 1                                 |
| Malposition            | 1                                 | -                                 |
| Iatrogenic sinus       | 1                                 | -                                 |
| Tumour overgrowth      | 2                                 | 3                                 |
| Stent migration        | 3                                 | -                                 |
| Recurrent fistula      | 2                                 | -                                 |
| Haematemesis           | 1                                 | -                                 |

Two patients died on days 4 and 7 respectively, while still in hospital. They succumbed to aspiration pneumonia. Survival was better in female patients, with a hazard ratio of 0.55. Pneumonia carried a significant hazard ratio of 10.86 ( $p = 0.010$ ).

**General**

For both groups of patients the dysphagia score improved significantly after stenting (McNemar’s test for symmetry,  $p < 0.001$  and  $p = 0.013$  respectively). Tumour overgrowth, which is a commonly reported complication, was infrequent in our group, affecting only 5/56 patients. All of these were successfully re-stented.

**Discussion**

Cancer of the oesophagus is epidemic in South Africa, with very few patients presenting at a resectable stage of the disease. Palliative options have now shown promise, with improvement of dysphagia and decreased morbidity with the use of SEMS.

The low frequency of tumour overgrowth may be the result of the method of follow-up as we relied on relatives to provide dates of death. Some of the patients died at home and the death may have been because of stent-related complications, but this aspect could not be investigated adequately. Stent migration did not pose a problem in the stricture group either, although it has been noted in other studies.<sup>2,7,13,15</sup>

During stenting 1 patient sustained an iatrogenic perforation. Oesophageal perforation in the absence of cancer is normally managed surgically but patients with malignancies are poor surgical candidates. White *et al.*<sup>16</sup> described stenting of iatrogenic perforations of oesophageal malignancies using SEMS. Immediate placement of a coated SEMS provided effective treatment with a survival range from 152 to 263 days. Unfortunately our patient was too ill to warrant further intervention.

Malignant TOF occurs in 5 - 15% of patients with oesophageal cancer, with major associated co-morbidities. A palliative goal should be to seal the fistula, and improve dysphagia and quality of life, with minimal co-morbidities. In our fistula group, median survival was 62 days, which is comparable to other studies (35 - 201 days).<sup>4,6,7,12,17-20</sup>

Despite the apparently striking difference in survival (62 days v. 91 days), a comparison of survival estimates using Kaplan-Meier curves (Fig. 1) showed no statistically significant difference ( $p = 0.9456$ ). One would have expected the TOF group to have had a shorter survival because of the presence of pneumonia in over half the cases, however this was not so. Multiple other studies<sup>4,7,17,19,20</sup> have also shown similar if not better median survival than ours, especially in the TOF group.

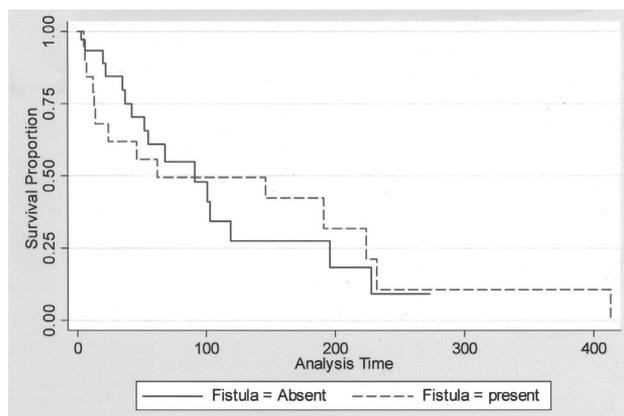


Fig. 1. Kaplan-Meier survival estimate comparing survival in the stricture group v. the TOF group ( $p = 0.945$ ).

We had 2 procedure-related complications but all our fistulas were sealed, which is comparable to other studies (80 - 100%).<sup>4,7,12,17,18</sup> Ramirez *et al.*<sup>22</sup> conducted a survey and found that although 75% of physicians had inserted fewer than 3 stents their overall procedural complication was 7%, which highlights the ease of insertion of SEMS even in a group with relatively little experience.

Our other complications (tumour overgrowth, recurrent fistula) were similar to other studies.<sup>2,4,7,12,17,21</sup> Common causes were tumour overgrowth or ingrowth, food impaction or granulation tissue formation, stent migration and stent covering disruption.<sup>17</sup> In 2 of our patients the recurrent fistulas were probably due to stent covering disruption as the stent position remained unchanged. Both patients were successfully re-stented.

Stent migration occurred in 3/21 patients. In 1 patient the stent migrated and passed through his digestive tract (confirmed radiologically). The patient presented with recurrent signs of TOF and was successfully re-stented. Studies<sup>7,13,14</sup> have suggested that covered stents have a higher incidence of migration because the polyethylene foil prevents tumour ingrowth which helps to anchor uncovered stents. We found similar results in our study, with no migration in the uncovered stent group.

Aspiration pneumonia, present in over half of the TOF patients at presentation, was clearly significant. Even with aggressive pre-stent antibiotics and physiotherapy, the effect of pneumonia on survival still remained statistically and clinically significant ( $p = 0.010$ , hazard ratio 10.86). Aspiration pneumonia remains an important cause of death in these patients.<sup>4,7,17</sup>

In general the symptoms were similar in both groups after stenting; chest pain and reflux were the most common. These were treated with analgesia and H<sub>2</sub>-antagonists respectively.

Antireflux stents are now available. Laasch *et al.*<sup>23</sup> compared open versus antireflux stents for distal oesophageal carcinoma and found that the antireflux stent significantly reduced symptomatic reflux, with only 4% of patients requiring treatment.

One patient presented with haematemesis requiring transfusion. Sarpay *et al.*<sup>12</sup> reported an incidence of 5%, similar to other studies.<sup>2,7,14,17</sup> Haematemesis could be the result of pressure necrosis, the natural progress of the disease, or trauma from the uncovered ends of the stent.<sup>2,7</sup>

Food impaction has been important in other centres,<sup>4,13,17, 21</sup> but we did not encounter this complication, perhaps because of the careful dietary counselling our patients receive. In saying this we should reiterate that possible poor follow-up may account for this complication not being apparent.

Although the first 4 patients had their stents placed under general anaesthesia, the rest were inserted under conscious sedation. We had no significant complications with sedation, and most patients tolerated the sedation well. Currently all stents are routinely inserted under sedation. Other authors<sup>1,4,6,7,12,13,17</sup> have used either general anaesthesia or sedation, but have shown no differences in outcome with either technique.

Of the other options, self-expandable plastic stents (SEPS) offer similar advantages to SEMS and were the treatment of choice before the advent of SEMS. In a review article Taal *et al.*<sup>24</sup> compared SEMS and SEPS and concluded that SEMS had fewer long-term complications and were therefore the palliative option of choice.

## Conclusions

In our hands SEMS has provided a viable, safe and effective option, which improves the quality of life of these terminally ill patients, with minimal morbidity. As the techniques and quality of stents improve, the survival rate may improve; at present SEMS remains our palliative option of choice.

## REFERENCES

- Patti M, Li R, Tedesco P, *et al.* Esophageal cancer. *Emedicine* 01/03/2006.
- Feins RH, Johnstone DW, Baronos ES, O'Neil SM. Palliation of inoperable esophageal carcinoma with the Wallstent endoprosthesis. *Ann Thorac Surg* 1996; 62: 1603-1607.
- Meunier B, Stasik C, Raoul JL, *et al.* Gastric bypass for malignant esophagotracheal fistula. *Eur J Cardiothorac Surg* 1998; 13: 184-189.
- Tomaselli F, Maier A, Sankin O, Woltsche M, Pinter H, Smolle-Jüttner FM. Successful endoscopic sealing of malignant esophagotracheal fistula by using a covered self-expandable stenting system. *Eur J Cardio-thorac Surg* 2001; 20: 734-738.
- Muto M, Ohtsu A, Miyamoto S, *et al.* Concurrent chemoradiotherapy for esophageal carcinoma patients with malignant fistulae. *Cancer* 1999; 86: 1406-1413.
- Alexander EP, Trachiotis GD, Lipman TO, Wadleigh RG. Evolving management and outcome of esophageal cancer with airway involvement. *Ann Thorac Surg* 2001; 71: 1640-1644.
- Kostopoulos PP, Zissis MI, Polydorou AA, *et al.* Are metal stents effective for palliation of malignant dysphagia and fistulas. *Dig Liver Dis* 2003; 35: 275-282.
- Lolley DM, Ray JF, Ransdell HT, Razzuk MA, Urschel HC. Management of malignant esophagorespiratory fistula. *Ann Thorac Surg* 1978; 25: 516-520.
- Chauhan SS, Long JD. Management of tracheoesophageal fistula in adults. *Curr Treat Options Gastroenterol* 2004; 7: 31-40.
- Symbas PN, McKeown PP, Hatcher CR jun., Vlasio SE. Tracheoesophageal fistula from carcinoma of the esophagus. *Ann Thorac Surg* 1984; 38: 382-386.
- Duranceau A, Jamieson GG. Malignant tracheoesophageal fistula. *Ann Thorac Surg* 1984; 37: 346-354.
- Sarpay A, Oz N, Cihangir C, Demircan A, Isin E. The efficacy of self-expanding metal stents for palliation of malignant esophageal strictures and fistulas. *Eur J Cardiothorac Surg* 2003; 23: 794-798.
- Christie NA, Buenaventura PO, Fernando HC, *et al.* Results of expandable metal stents for malignant esophageal obstruction in 100 patients: short-term and long-term follow-up. *Ann Thorac Surg* 2001; 72: 1797-1802.
- Lee SH. The role of oesophageal stenting in the non-surgical management of oesophageal stricture. *Br J Radiol* 2001; 74: 891-900.
- Riccioni ME, Shah SK, Tringali A, *et al.* Endoscopic palliation of unresectable malignant esophageal strictures with self-expanding metal stents: comparing ultraflex and esophagocoil stents. *Dig Liver Dis* 2002; 34: 356-363.
- White RE, Mungatana C, Topazian M. Expandable stents for iatrogenic perforation of esophageal malignancies. *J Gastrointest Surg* 2003; 7: 715-719.
- Shin JH, Song HY, Ko GY, Lim JO, Yoon HK, Sung KB. Esophagorespiratory fistula: long-term results of palliative treatment with covered expandable metallic stents in 61 patients. *Radiology* 2004; 232: 252-259.
- May A, Ell C. Palliative treatment of malignant esophagorespiratory fistulas with Gianturco-Z stents. *Am J Gastroenterol* 1998; 93: 532-535.
- Rajjman I, Lynch P. Coated expandable esophageal stents in the treatment of digestive-respiratory fistulas. *Am J Gastroenterol* 1997; 92: 2188-2191.
- Rajjman I, Siddique I, Ajani J, Lynch P. Palliation of malignant dysphagia and fistulae with coated expandable metal stents: Experience with 101 patients. *Gastrointest Endosc* 1998; 48: 172-179.
- Wu WC, Katon RM, Saxon RR, *et al.* Silicone-covered self-expanding metallic stents for the palliation of malignant esophageal obstruction and esophagorespiratory fistulas. Experience in 32 patients and a review of the literature. *Gastrointest Endosc* 1994; 40: 22-23.
- Ramirez FC, Dennert B, Zierer ST, Sanowski RA. Esophageal self-expandable metallic stents – indications, practices, technique and complications: Results of a national survey. *Gastrointest Endosc* 1997; 75: 360-364.
- Laasch HU, Marriott A, Wilbraham L, Tunnah S, England RE, Martin DF. Effectiveness of open versus antireflux stents for palliation of distal esophageal carcinoma and prevention of symptomatic gastroesophageal reflux. *Radiology* 2002; 225: 359-365.
- Taal BG, Kooyman VM, Boot H. Expandable stents compared to conventional plastic endoprotheses in malignant oesophageal obstruction, especially in cardiac cancer and fistulas: the experience of the Netherlands Cancer Institute. *Eur J Gastroenterol* 1998; 10: 745-752.