

Palliative treatment of advanced esophageal cancer with metal-covered expandable stents. A cost-effectiveness and quality of life study

D. Xinopoulos¹, D. Dimitroulopoulos¹, K. Tsamakidis¹, D. Korkolis², A. Fotopoulou³, A. Bazinis⁴, M. Kontis⁴, P. Vasilopoulos², E. Paraskevas¹

¹Gastroenterology Unit; ²1st Department of Surgical Oncology; ³1st Department of Radiation Oncology; ⁴Psychiatric Department; ⁵Economics and Statistics Department, "Agios Savvas" Cancer Hospital, Athens, Greece

Summary

Purpose: The aim of this retrospective study was to evaluate the efficacy and safety of endoscopic therapy with self-expanding metallic endoprotheses in the management of inoperable primary malignant esophageal obstruction or stenosis and the cost-effectiveness of the method.

Patients and methods: Between 5/1997-12/2002, obstruction of the esophagus was diagnosed in 78 patients (52 males, 26 females, age range 53-102, mean 72.3 years). The etiology was squamous cell carcinoma (n=42) and adenocarcinoma of the oesophagus (n=36). In total, 89 ultraflex metal stents were introduced endoscopically. In 46 patients dilation with Savary dilators prior to stent placement was required. A cost-effective analysis was performed, comparing oesophageal stenting with laser therapy.

Results: Stents were placed successfully in all patients. After 48 h, all patients were able to tolerate solid

or semi-solid food. During the follow-up period 8 patients developed dysphagia due to food impaction (treated successfully endoscopically). Eleven patients developed recurrent dysphagia 4-16 weeks after stenting due to tumor overgrowth and were treated with placement of a second stent. The median survival time was 18 weeks. There was no survival difference between squamous cell and adenocarcinoma of the esophagus. A similar cost was calculated for both procedures. A significant improvement in quality of life was noted in patients undergoing stenting (96% and 75% vs. 71% and 57% for the first two months).

Conclusion: Placement of self-expanding metal stents is a safe and cost-effective treatment modality that improves the quality of life, compared with laser therapy, for patients with inoperable malignant esophageal obstruction.

Key words: cost-effectiveness, esophageal cancer, metal stents, palliation, quality of life, survival

Introduction

Approximately 50-60% of patients with esophageal cancer have advanced disease at the time of presentation and are suitable only for palliation of dysphagia [1]. Surgery is unsuitable for palliation be-

cause of high morbidity [1,2]. Radiotherapy can cause a temporary increase in dysphagia and has short-lasting effects [3,4]. Chemotherapy alone is not an effective method of palliation but can be a useful adjunct to laser therapy [5]. Rigid plastic endoprotheses are associated with complications in up to 36% of patients, including esophageal perforation, hemorrhage, tube dislodgment, aspiration pneumonia, and pressure necrosis [6-9]. In addition, the vast majority of patients can tolerate only a liquid or semisolid diet after insertion of a plastic endoprosthesis because of the rigidity and small lumen of the device. Laser therapy is a useful palliative treatment and is associated with fewer complications than intubation [10], but must be repeated frequently.

Self-expandable metallic stents are very effective in the palliation of symptomatic esophageal malignant neoplasms [11-21] and are associated with a shorter

Received 19-07-2005; Accepted 27-08-2005

Author and address for correspondence:

Dimitrios Dimitroulopoulos, MD
Parnassou 35 street
Halandri
152 34 Athens
Greece
Tel: +30 210 6892460
E-mail: dimdim@otenet.gr

hospital stay and fewer fatal complications than plastic stents [13]. Metal endoprotheses can usually be introduced with the patient under a conscious sedation and local anesthesia. After stenting, the patients can eat solid food. Covered metal stents are excellent for sealing esophageal perforations and fistulas and also are more effective than laser treatment in palliating malignant dysphagia [22].

The aim of the present study was to assess the efficacy and safety of these stents, to study the natural course of esophageal malignancies after stent placement and to compare the method as to cost-effectiveness and quality of life with endoscopic laser therapy.

Patients and methods

A retrospective analysis of all patients with inoperable esophageal cancer treated with either endoprosthesis or laser palliation was carried out. The second group was included only for cost-effective analysis, since selection was not done randomly.

A. Endoprosthesis group

From May 1997 to December 2002, 78 patients underwent placement of 89 highly flexible knitted, self-expanding metal stents (Ultraflex Esophageal Prostheses, Microvasive, Inc., Natick, MA). There were 52 men and 26 women with mean age 72.3 years (range 53-102).

The etiology of obstruction was squamous cell carcinoma in 42 patients and adenocarcinoma of the esophagus in 36 patients.

The site of obstruction was located in the upper third of the esophagus in one patient (squamous cell cancer), in the middle third in 38 patients (37 squamous cell cancer, 1 adenocarcinoma) and in the lower third in 39 patients (4 squamous cell cancer, 35 adenocarcinoma). In 16 cases the esophagogastric junction was also involved. Four patients had broncho-esophageal fistulas. All cases were considered inoperable either because they had end-stage disease with extensive primary local tumor or because of the presence of distant metastases or poor general status.

The length of the stenosis varied from 3.5 to 7.2 cm (mean 4.7 ± 1.9 cm).

Dysphagia was graded on a 5-point scale (I=no dysphagia, II=dysphagia to normal solids, III=dysphagia to soft solids, IV=dysphagia to solids and liquids, V=complete dysphagia, even to saliva). Thirty-three patients (42%) had grade II-III, 33 (42%) had grade IV and 12 patients (16%) had grade V dysphagia. The

scoring system was slightly modified from that described by Mellow and Pincas [23].

Before stenting, an esophagogram was obtained to determine the precise length of the stenosis and the presence or not of broncho-esophageal fistulas.

In 46 (59%) patients the precise length of stenosis was not clear in the esophagogram and these patients underwent esophageal dilation using Savary dilators over a stiff-angled metallic guide wire. The stenosis was dilated to 12.8 or 15 mm, under image intensifier control.

After dilation, the position and length of the stenosis was defined endoscopically and the upper and lower margins of the stenosis were marked under fluoroscopic guidance with external radiopaque markers. Using these radiopaque markers as a guide, and under fluoroscopic control, endoprosthesis was deployed.

A plain chest radiography was obtained a few minutes after placement to assess expansion of the stent. If the positioning of the stent was satisfactory and flow of barium into the stomach was unimpaired, esophagoscopy was performed after 48 h to document patency of the stented esophageal lumen and to confirm the final accurate position of the stent. The dysphagia score was estimated during outpatient visits every 4 weeks until patient's death.

Informed consent was obtained from all patients, according to bioethical principles in medical research and the declaration of Helsinki (Revised 1983).

B. Laser group

A second group of 27 patients (18 men, 9 women, aged 63-89 years, mean 71.8 years) with surgically incurable esophageal cancer treated endoscopically with Nd:Yag or Diomed laser for palliation of esophageal obstruction during the period September 1996-March 1999, were selected for comparison in the cost-effective analysis. The site of obstruction was located in the middle third of the esophagus in 8 patients (all squamous cell cancer) and in the lower third in 19 patients (1 squamous cell cancer and 18 adenocarcinoma). In 13 cases the esophagogastric junction was included.

Prior to the first laser session, dilation of the esophagus was performed; 2-6 laser sessions (mean 4) were required until ability to swallow, at least semisolid food, was achieved.

Apart from the first sessions, the other laser sessions were performed on an outpatient basis with frequency depending on the progress of obstruction. Clinical and endoscopic follow up were performed monthly.

Light energy per session ranged between 1,200-17,000 joules (mean 4500).

Statistical analysis

Dysphagia scoring before and after stenting were compared by the paired Student's-*t* test. Survival was estimated by constructing Kaplan-Meier curves [24]. Differences in survival between groups were assessed by the log-rank test.

Cost-effective analysis

A cost-effective analysis was performed comparing esophageal stenting with laser therapy in patients with primary esophageal cancer.

The cost of each procedure (stenting-laser therapy) was calculated by taking into account:

1. The personnel costs: these were calculated as the cost of a working hour for each person (physician, technician, nurse, assistant personnel).

2. The cost of materials: stents, drugs, contrast liquids, films and liquids for film processing.

3. The equipment cost calculated in working hours. A yearly payment on an annuity basis at 8% and a term of 5 years and 8 years was used to calculate the cost of endoscopic equipment/lasers/Savary dilators and radiologic equipment respectively. The prices of equipment were those of the year 2000.

4. The housing and overhead costs based on the number of square meters required to investigate and treat a patient, including the cost of furniture, cleaning, telephone and services of various overhead departments. In the overall cost, hospitalization per day of stay for each patient was added.

Costs were built up from a database of health care cost elements in Greece and from the currently applicable prices of Ultraflex esophageal stents.

For the group of patients treated with introspective laser application, the same methodology for estimation of quality of life was followed.

Quality of life

The quality of life assessment was performed by a psychiatrist, experienced in oncologic patients and was based on the QLQ-C30 questionnaire proposed by EORTC [25].

Questionnaires were completed without any conscious influence or help, during interviews in which all symptoms, co-morbidity and any additional palliative medication were assessed: 1) at baseline, within one week before therapy; 2) after one month; 3) after 2 months. Before analysis, raw scores were linearly transformed to scales of 0 to 100.

The study included 70 patients that underwent

stent placement (the remaining 8 had passed away or were unable due to the critical situation of their health at the end of the first month of the follow-up period) and all patients of the laser group.

Results

A. Endoprosthesis group

Stenting was technically successful in all patients, and was determined endoscopically and fluoroscopically. All stents were placed beyond the tumor stenosis, at least 10 mm from the proximal and distal ends. The mean duration of the procedure was 28 min. Mean inpatient stay after stenting was 3.2 ± 1 days.

Forty-eight hours after endoprosthesis placement all patients were able to tolerate a solid or semi-solid diet. No procedure-related mortalities or major complications occurred (aspiration, bleeding, perforation or misplacement of the stent). Stents were well tolerated with no foreign-body sensation. Only one patient experienced a side effect, immediately after endoprosthesis placement (chest pain, fever, leucocytosis) without any radiologic signs of mediastinitis. He responded to antibiotics within 48 h.

Sealing of the esophagorespiratory fistulas and relief from symptoms of aspiration were achieved in all patients with broncho-esophageal communications. The mean dysphagia score of 2.91 ± 0.36 before stenting, improved to a mean score of 1.17 after endoprosthesis placement ($p=0.04$).

One stent, in a case involving esophagogastric junction, migrated into the stomach 3 weeks after placement and was replaced by a new Flamingo type stent.

Further weight loss was controlled in all patients, except in 8 who died 4-6 weeks after stenting due to advanced malignant disease. The others gained between 1 and 6.3 kg of body weight.

During the follow up period 8 patients developed dysphagia due to food impaction that was successfully treated endoscopically. Eleven (14%) patients experienced recurrent dysphagia 4-16 weeks after stenting, due to tumor overgrowth. The primary tumor was squamous cell carcinoma (5 of middle and one of the lower esophagus) in 6 patients and adenocarcinoma of lower esophagus in 5, including esophagogastric junction in 3 cases. In these patients a second stent was implanted to improve swallowing.

Median overall survival was 18 weeks (95% CI 16-20). When patients with adenocarcinoma were separately analyzed from those with squamous cell car-

cinoma, no difference in survival could be established (median 18 weeks, 95% CI 16-20 and 19 weeks, 95% CI 15-23, respectively) (Figure 1).

B. Laser group

Mean hospitalization time for the first laser esophageal patency was 13.4±1 days.

The therapeutic effect of each laser round lasted 3-10 weeks (mean 4.8).

Complications occurred in 2 out of 27 patients (one fatal due to uncontrollable tumor bleeding and one minor perforation in a case of lower esophageal obstruction).

The mean survival time for patients that received laser therapy was 17 weeks (95% CI 15-19 weeks) and was similar to the mean survival time of patients that underwent stenting. A mean number of 12 laser sessions per patient was performed.

C. Cost-effectiveness and quality of life analysis

A similar cost was calculated for both procedures (Table 1). The overall cost of stenting per patient was 3,103 Euro and the overall cost of laser therapy per patient was 2,947 Euro. Mean hospitalization time was 3.2±1 days for the group that underwent stent placement.

Although the evaluation of quality of life is very difficult, the quality of life questionnaire analysis showed a significant improvement of a well-being status in patients of the stenting group.

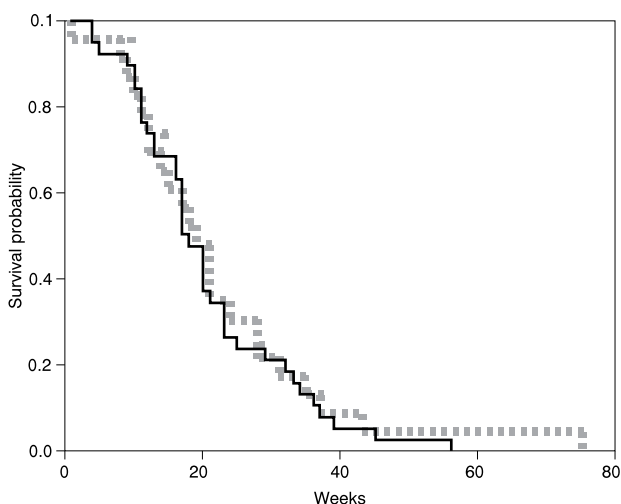


Figure 1. Kaplan-Meier estimated survival curve for 42 stented patients with squamous cell carcinoma (—) and 36 stented patients with adenocarcinoma of the oesophagus (-----).

Table 1. Estimated procedural total costs per patient in Euros

Costs	Endoprosthesis group	Laser palliation group
Salaries	37	99
Hospitalization	452	1,893
Consumables	2,504	482
Housing overhead equipment	110	473
Total	3,103	2,947

The percentage of patients having major problems on the QLQ-C30 scales at the baseline was similar in both groups (88% of subjects with stent placement and 91% in the laser group). The most prominent features were problems in strenuous activity, limitations in work performance and hobbies, worrying, depression and interference in family and social life in scales concerning function ability and fatigue, nausea, vomiting, sleeping trouble and lack of appetite in scales concerning symptoms.

Comparing the baseline score with the 1- and 2-month scores, a significant improvement was noted in patients of the stented group (96% and 75% vs. 71% and 54% in the laser group), in matters mainly concerning emotional and social functioning, vomiting and additional symptoms.

After the first month, a progressive decrease on global health/quality of life was observed in both groups according to the analogic scales of the QLQ-C30 questionnaire. Also lower scores in physical and role functioning and higher values in fatigue and pain were noted, as expected.

Discussion

The vast majority of patients with esophageal cancer will not be surgical candidates at the time of diagnosis either because of advanced disease or the presence of significant comorbidities [26].

After the first publication by Domschke et al. [27], several authors have reported excellent relief of dysphagia with implantation of self-expandable metal stents [3,28-31]. The results of published series show immediate technical success of 100% with improvement in the dysphagia score from 83 to 100% of the patients [22,32,33]. These results are similar to those reported in the present study. In our study the average cost of palliation with metal stents was found similar to that of palliation with endoscopic laser application. Comparing stenting with BICAP diathermy, alcohol injection and Atkinson tube insertion, Nicholson et al.

reported that the average cost was much lower in the metal stent group [34].

Although it is safer and easier to place expandable stents, these devices are not devoid of complications. The main complication of metal stents is distal migration, with an incidence rate ranging between 10 and 30% of the cases [35]. Migration is most common (50%) when covered endoprotheses are used to treat distal esophageal lesions involving the gastroesophageal junction [36,37]. If a stent migrates completely into the stomach, it should be removed endoscopically or via a small gastrotomy [38]. If a stent migrates partially, insertion of a second uncovered stent can prevent further movement [29]. Replacement of a totally or partially displaced stent is a common and safe technique with optimal results.

In our study only one Ultraflex stent migrated into the stomach 3 weeks after placement. Stent migration incidence was therefore much less in our series than previously reported [35]. It was replaced with a new Flamingo type stent. These conical covered esophageal stents are a relatively new type of stents, with a significant lower rate of distal migration [39]. They are indicated for lesions involving the esophagogastric junction.

Another problem with esophageal stents is tumor ingrowth through the stent mesh (uncovered), which occurs in 17-36% of the cases or overgrowth (covered) in as many as 9% of the cases [40,41]. Eleven out of 78 patients in our study experienced this problem, but were able to overcome recurrent dysphagia by placement of additional stents as previously reported [29].

An uncommon complication of stenting is usually a mild and self-limiting haemorrhage. Perforation of the esophagus as procedural complication is very rare [33]. Both of them were not present in our series. Esophageal pain after stenting is common but usually resolves in a few days.

The value of any cancer therapy must be determined by the observed tumor response, the impact on survival, the occurrence of side-effects and the cost and effect of treatment on quality of life.

One major question, still unresolved, is whether placement of stents improves survival of these patients. Our results indicate that palliation is the only effect one can expect from stenting. Overall survival rates were very poor with a median survival of only 18 weeks. Most importantly, survival was equally poor in both squamous cell and esophageal adenocarcinoma patients. Comparing the overall cost of the method with the overall cost of endoscopic laser therapy, a technique proved effective and characterized by low complication rates, a small difference of only 156 Euros was noted.

Taking into account the improvement of quality of life, although for few weeks, we conclude that stenting is a safe and effective palliative method for the treatment of dysphagia due to esophageal cancer, improving quality of life more than other palliative options, characterized by a similar overall cost.

References

1. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: a critical review of surgery. *Br J Surg* 1980; 67: 381-390.
2. Muller JM, Erasmi H, Stelzner M et al. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; 77: 845-857.
3. Hishikawa Y, Kamikonya N, Tanaka S et al. Radiotherapy of esophageal carcinoma: role of high-dose-rate intracavitary irradiation. *Radiother Oncol* 1987; 9: 13-20.
4. Caspers RJ, Welvaart K, Verkes RJ. The effect of radiotherapy on dysphagia and survival in patients with esophageal cancer. *Radiother Oncol* 1988; 12: 15-23.
5. Highley MS, Parnis FX, Trotter GA et al. Combination chemotherapy with epirubicin, cisplatin and 5-fluorouracil for the palliation of advanced gastric and oesophageal carcinoma. *Br J Surg* 1994; 81: 1763-1765.
6. Atkinson M, Ferguson R, Parker GC. Tube introducer and modified Celestin tube for use in palliative intubation of esophago-gastric neoplasms at fiberoptic endoscopy. *Gut* 1978; 19: 669-671.
7. Loizou LA, Grigg D, Atkinson M et al. A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. *Gastroenterology* 1991; 100: 1303-1310.
8. Tytgat GN. Endoscopic review of esophageal cancer: possibilities and limitations. *Endoscopy* 1990; 22: 263-267.
9. Fuegger R, Niederle B, Jantsch H et al. Endoscopic tube implantation for the palliation of malignant esophageal stenosis. *Endoscopy* 1990; 22: 101-104.
10. Mason RC, Bright N, McColl I. Palliation of malignant dysphagia with laser therapy: predictability of results. *Br J Surg* 1991; 78: 1346-1347.
11. Song HY, Choi KC, Cho BH et al. Esophago-gastric neoplasms: palliation with a modified Gianturco stent. *Radiology* 1991; 180: 349-354.
12. Schaer J, Katon RM, Ivancev K et al. Treatment of malignant esophageal obstruction with silicone-coated metallic self-expanding stents. *Gastrointest Endosc* 1992; 38: 7-11.
13. Knyrim K, Wagner HJ, Bethge N et al. A controlled trial of an expandable metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med* 1993; 329: 1302-1307.
14. Cwikiel W, Stridbeck H, Tranberg KG et al. Malignant esophageal strictures: treatment with a self-expanding nitinol stent. *Radiology* 1993; 187: 661-665.
15. Wu WC, Katon RM, Saxon RM et al. Silicone covered self-expandable metallic stents for the palliation of malignant oesophageal obstruction and esophago-respiratory fistulas: experience in 32 patients and a review of the literature. *Gastrointest Endosc* 1994; 40: 22-23.
16. Song HY, Do YS, Sung KB et al. Expandable esophageal

- metallic stents: experience in 104 patients. *Radiology* 1993; 189(P): 177 (abstr).
17. Maeda M. Oesophageal spiral Z-stents. In: Proceedings of the Western Angiographic and Interventional Society Portland, OR: Western Angiographic and Interventional Society, 1993: 81 (abstr).
 18. Saxon RR, Barton RE, Rösch J. Complications of esophageal stenting and balloon dilatation. *Semin Intervent Radiol* 1994; 11: 276-282.
 19. Song HY, Choi KC, Kwon HC et al. Esophageal strictures: treatment with a new design of a modified Gianturco stent. *Radiology* 1993; 184: 729-734.
 20. Ellul J, Watkinson AF, Khan R et al. Self-expandable metallic stents for the palliation of dysphagia due to inoperable oesophageal carcinoma. *Br J Surg* 1995; 82: 1678-1681.
 21. Adam A, Chetty N, Roddie M et al. Self-expandable stainless steel endoprosthesis for the treatment of malignant bile duct obstruction. *AJR* 1990; 156: 321-325.
 22. Adam A, Morgan R, Ellul J et al. A new design of the esophageal Wallstent endoprosthesis resistant to distal migration. *AJR* 1998; 170: 1477-1481.
 23. Mellow MH, Pinkas H. Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction: analysis of technical and functional efficacy. *Arch Intern Med* 1985; 145: 1443-1446.
 24. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1959; 53: 457-481.
 25. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365-376.
 26. Lambert R. An overview of the management of cancer of the esophagus. *Gastrointest Endosc Clin N Am* 1998; 8: 415-434.
 27. Domschke W, Foerster ECh, Matek W et al. Self-expanding mesh stent for esophageal cancer stenosis. *Endoscopy* 1990; 22: 134-136.
 28. Lambert R. Treatment of esophagogastric tumors. *Endoscopy* 2003; 35: 118-126.
 29. McManus K, Khan I, McGuigan J. Self-expanding oesophageal stents: strategies for re-intervention. *Endoscopy* 2001; 33: 601-604.
 30. Singhvi R, Abbasakoor F, Manson JM. Insertion of self-expanding metal stents for malignant dysphagia: assessment of a simple endoscopic method. *Ann R Coll Surg Engl* 2000; 82: 243-248.
 31. Takkanen VJ, Nemlander AT, Ramo OJ et al. Expandable metallic stents in the management of malignant oesophageal obstruction. *Ann Chir Gynaecol* 2000; 89: 20-23.
 32. Siersema PD, Marcon N, Vakil N. Metal stents for tumors of the distal esophagus and the gastric cardia. *Endoscopy* 2003; 35: 79-85.
 33. Lee SH. The role of oesophageal stenting in the non-surgical management of oesophageal strictures. *Br J Radiol* 2001; 74: 891-900.
 34. Nicholson DA, Haycox A, Kay CL et al. The cost effectiveness of metal oesophageal stenting in malignant disease compared with conventional therapy. *Clin Radiol* 1999; 54: 212-215.
 35. Cowling MG, Mason RC, Adam AN. Esophageal and upper GI stenting. *Radiology* 1999; 2: 2-7.
 36. Warren WH. Palliation of dysphagia. *Chest Surg Clin N Am* 2000; 10: 605-623.
 37. Laasch HU, Marriott A, Wilbraham L et al. Effectiveness of open versus antireflux stents for palliation of distal esophageal carcinoma and prevention of symptomatic gastroesophageal reflux. *Radiology* 2002; 225: 359-365.
 38. Watkinson AF, Ellul J, Entwisle K et al. Oesophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprosthesis. *Radiology* 1995; 195: 821-827.
 39. Sabharwal T, Hamady MS, Chui S et al. A randomised prospective comparison of the Flamingo Wallstent and Ultraflex stent for palliation of dysphagia associated with lower third oesophageal carcinoma. *Gut* 2003; 52: 922-926.
 40. Rozanes I, Poyanli A, Acunas B. Palliative treatment of inoperable malignant esophageal strictures with metal stents: one center's experience with four different stents. *Eur J Radiol* 2002; 43: 196-203.
 41. Mc Grath JP, Browne M, Riordan C et al. Expandable metal stents in the palliation of malignant dysphagia and oesophageal-respiratory fistulae. *Ir Med J* 2001; 94: 270-272.