EXPANDABLE METAL STENTS FOR INOPERABLE OESOPHAGEAL CANCER

A West Midlands Health Technology Assessment Collaboration report

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West Midlands Health Technology Assessment Collaboration (WMHTAC)

The WMHTAC produces rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Health Authorities. Reviews take approximately 6 months and aim to give a timely and accurate analysis of the available evidence, with an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

Contributions of authors

Roger Gajraj liaised with experts, searched and independently extracted data from the literature, critically appraised the effectiveness data, conducted the economic analysis and wrote the report. Beti-Wyn Jones also independently assessed study quality and extracted data from included studies. David Moore and Fujian Song provided advice and support at all stages of this work and commented on draft versions of the report.

Conflicts of interest

This work has been undertaken by people funded by the NHS. The authors have received no funding from any sponsor in this work.

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West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the use of Expandable metal stents for inoperable oesophageal cancer was:

Supported

The conclusions of the report showed that SEMS offer marginal benefits when compared to plastic tubes, and these benefits are associated with a small additional cost.

Anticipated expiry date: January 2004

- This report was completed in February 2003
- The searches were completed in August 2002

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1. EXECUTIVE SUMMARY

Description of proposed service
The use of self-expanding metal stents (SEMS) for dysphagia relief in patients with inoperable oesophageal cancer is already established clinical practice. SEMS is a relatively costly device that has largely replaced the cheaper semi-rigid plastic tubes.

Epidemiology and background
Oesophageal cancer is the eighth commonest cancer in Britain and the fifth commonest cause of death from cancer. There are about 650 new cases each year in the West Midlands. The prognosis is poor with 5-year survival rates of 9%. About 200-250 endoprostheses are inserted every year for palliation of dysphagia in West Midlands residents. One in five West Midlands providers still use plastic tubes but do so on an occasional basis only.

Studies included in the review
Six small RCTs compared SEMS with plastic tubes. Considerable bias may have resulted in all six studies from differential treatment of randomised groups (greater oesophageal dilation of patients randomised to plastic tubes). The direction of evidence was in favour of SEMS.

Summary of benefits
The benefits of SEMS compared to plastic tubes were significantly lower (by 11%) major complications; significantly lower (9%) procedure-related mortality; 7% lower 30-day mortality; greater *initial* improvement in dysphagia; shorter hospitalisation; and 24 days longer survival. Quality of life was similar.

Costs
The average hospital cost of inserting a plastic tube is about £1,610; corresponding averages for covered SEMS are £2,220 and for uncovered SEMS £1,970. The use of SEMS costs the West Midlands secondary health care sector an extra £140,000 each year.

Cost-effectiveness
Covered SEMS cost on average £7,630 per life-year saved and about £880 for an added 1-point improvement in dysphagia score. Uncovered SEMS cost on average £7,920 per life-year saved and about £1,430 for an added 1-point improvement in dysphagia score.

Other implications
Substantially improved outcomes could possibly result if less oesophageal dilation was employed during insertion of plastic tubes. Conversely, the ease of insertion of SEMS could result in greater clinical and economic benefits in everyday practice compared to those observed in clinical trials.

Conclusions
There is good evidence that SEMS are cost-effective and fair evidence that they are superior to plastic stents.

LIST OF ABBREVIATIONS

ARIF- Aggressive Research Intelligence Facility
DARE-Database of Abstracts of Reviews of Effectiveness
EBRT- external beam radiotherapy
GI- gastro-intestinal
GOJ- gastro-oesophageal junction
HDU- high dependency unit
HES- Hospital Episode Statistics
ID- internal diameter
ITT- intention to treat
NHS EED- NHS Economic Evaluation Database
QoL- quality of life
RCT- randomised controlled trial
SEMS- self-expanding metal stent
UOS- upper oesophageal sphincter
WMHTAC- West Midlands Health Technology Assessment Collaboration

2. Aim of the review

The aim of this review was to assess the effectiveness and cost-effectiveness of self-expanding metal stents (SEMS) compared to semi-rigid plastic tubes in patients with inoperable oesophageal cancer.

In 1998 commissioners from two of the West Midlands health region's previous District Health Authorities identified variations in oesophageal cancer management and requested assistance from ARIF to identify cost-effective interventions. There were no general reviews on the management but one systematic review assessed the role of chemotherapy.[1] There was also limited evidence from randomised controlled trials (RCTs) regarding the effectiveness of different interventions.

Much of the adverse impact on quality of life derives from the dysphagia produced by the tumour and a variety of palliative interventions, including endoprosthesis insertion, are used in patients who are not eligible for surgery. Self-expanding metallic stents (SEMS) have largely replaced the older plastic tubes for oesophageal stenting. SEMS are considerably more expensive than plastic tubes but this may be offset by a lower rate of complications with shorter hospitalisation and consequently lower overall costs. WMHTAC therefore decided to undertake a systematic review and economic evaluation of SEMS compared to plastic tubes for patients with inoperable oesophageal cancer.

3. Background

3.1 Oesophageal cancer

3.1.1 Anatomy and histology

The oesophagus, approximately 26cm long in adults, is the part of the gastro-intestinal tract that extends from the oral cavity to the stomach. Squamous cell carcinoma predominates in the upper two-thirds of the oesophagus and adenocarcinoma arises in the lower third. The gastro-oesophageal junction (GOJ) comprises the most distal part of the oesophagus and the proximal part of the gastric cardia, the latter containing the cardiac sphincter which protects the oesophagus from regurgitation of gastric contents. Tumours arising in the GOJ have been subdivided into distal oesophageal adenocarcinoma, true carcinoma of the cardia and subcardial gastric cancer infiltrating the distal oesophagus,[2] but GOJ tumours are similar to those of the lower oesophagus and probably represent the same disease.[3] Metaplasia (Barrett's oesophagus) arises in the GOJ as a result presumably of gastric reflux and may progress histologically to dysplasia and then to adenocarcinoma.

3.1.2 Risk factors for oesophageal cancer

The two histological varieties of oesophageal cancer each possess different risk factors.

<u>Squamous cell cancer</u>

Tobacco smoking and excessive alcohol consumption act independently and synergistically to increase the risk for developing squamous cell oesophageal cancer.[4] Other risk factors include dietary zinc deficiency, preserved and pickled foods, human papillomavirus, certain rare inherited conditions such as Tylosis, untreated achalasia and coeliac disease.[5,6]

Adenocarcinoma

Oesophagitis caused by gastro-oesophageal reflux disease is one of the commonest medical conditions with 30% of adults in Western countries complaining of heartburn at least once per month.[7] Approximately 10% of patients with reflux-induced oesophagitis will develop metaplastic changes (Barrett's oesophagus).[7] Most or all cases of adenocarcinoma arise from areas of metaplasia; 2-5% of patients with Barrett's oesophagus will develop adenocarcinoma.[5]

Risk factors for malignant change of Barrett's metaplasia include male gender, increasing age, longer segments of metaplasia, severity and chronicity of reflux, white race, obesity, family history of gastric cancer, drug therapy (nitrates, benzodiazepines, anticholinergics and theophyllines), absence of *Helicobacter pylori* infection, cigarette smoking and low consumption of fruit and vegetables.[5,8,9]

3.1.3 Prevalence and incidence

Age and sex

Oesophageal cancer is the eighth most common cancer in the UK.[5] Incidence rates increase with age, peaking at 70-74years in both men and women, with a male:female ratio of cases of 4:3.[5] The incidence rate (per 100,000/yr) of oesophageal cancer in England & Wales (1993-96 registrations) was 14.0 in men and 9.2 in women.[10]

Geographical distribution

There is greater geographical variation in world-wide incidence of oesophageal cancer than any other cancer.[11] It is also the eighth most common cancer world-wide, with 80% arising in developing countries.[12] Areas of high risk include Southern and Eastern Africa, China, Southern Asia and South America.[12] Striking differences between local areas of the same region and between different ethnic groups within regions suggest that the majority of cases could be prevented by addressing environmental and lifestyle factors.[5,13]

Among European countries British men have the second highest incidence of oesophageal cancer and British women, with rates more than nine times higher than Greek women, have the highest incidence.[14]

Ethnic variation

Black Americans have a greater risk of developing squamous cell oesophageal cancer than whites[15] but the reverse is true for adenocarcinoma.[16]

Trends

The incidence of oesophageal cancer in the UK is increasing, in contrast to that of other upper gastro-intestinal (stomach and pancreas) malignancies.[9] While small increases[17] or decreases[18] have been reported for squamous cell cancer, many countries all report large increases for adenocarcinoma.[17-23] Particularly rapid

increases have occurred for GOJ adenocarcinomas[18,24] due to increased prevalence of multiple risk factors[18,25-27] or to changes in diagnosis and/or coding of GOJ tumours.[28,29]

3.1.4 Clinical presentation

Dysphagia is the commonest symptom first recognised by patients and is present in 75% of cases.[5] However, the oesophagus is a distensable organ and 50% of the luminal diameter may become compromised before patients perceive a problem.[30] Therefore, patients present late and the prognosis is consequently very poor.[9,30] Other common symptoms include dyspepsia, weight loss, vomiting, indigestion and a persistent cough.[5,13]

3.1.5 Diagnosis and assessment

Diagnosis

Oesophago-gastroscopy is now the main diagnostic investigation used, since a histopathological specimen can be obtained simultaneously to confirm the diagnosis and to direct the choice of surgical approach and lymph node clearance.[5] Barium swallow may be associated with a higher frequency of false positives and false negatives than endoscopy,[31,32] but is the first choice for identifying very proximal tumours, is well tolerated and still used commonly.[5]

Assessment

After confirming the diagnosis, staging of the tumour is necessary to assist in determining prognosis and whether radical interventions, including surgery, are indicated. The TNM classification is recommended and is based on the depth of tumour (T), regional lymph node involvement (N) and distant metastases (M).[33] Computerised tomography (CT) scans of the abdomen are necessary for detecting hepatic metastases.[5] Endoscopic ultrasound is the investigation of choice to assess local thoracic spread (the T stage) and operability of the tumour[5,34] and complements CT scans in assessing regional lymph node involvement.[35] Peritoneal involvement by GOJ tumours can be determined by laparoscopy.[5] More recent developments include positron emission tomography which is superior to CT scans in assessing regional lymph node involvement, and minimally invasive staging procedures such as lymph node biopsy using endoscopically guided ultrasonography.[35] The role of magnetic resonance imaging in the staging of oesophageal tumours is limited.[35]

3.1.6 Management of oesophageal cancer

Treatment is based on the stage of disease at presentation and the patient's general level of fitness. Patients with localised disease may be offered radical interventions (oesophagectomy, chemo-radiotherapy or multi-modality treatment involving chemo-radiotherapy followed by surgery) which offer the hope of a cure or long-term survival.[13] About two-thirds of patients have advanced disease at diagnosis unsuitable for radical interventions and most require palliative interventions for dysphagia.

Radical interventions

Surgery

Surgery is regarded widely as the only intervention that offers any realistic hope of a cure,[5,13] probably only for the very few patients in whom all gross disease can be removed en bloc with an envelope of normal tissue.[35] A distinction should therefore

be made between *curability* and *resectability* (i.e. where surgery or other radical intervention offers the hope of long-term survival).[35] Lesions without metastatic spread or mediastinal invasion are generally treated with oesophagectomy,[36] although the aggressiveness of the individual surgeon determines partially the decision to operate.[35]

Reductions in peri-operative mortality has been postulated as the reason for improving survival rates between 1971-90.[5] Neoadjuvant (preoperative) chemotherapy (Medical Research Council trial OEO2)[9] and adjuvant chemo-radiotherapy (in adenocarcinoma of the GOJ)[37] have been shown to improve survival after potentially curative surgery. It is now generally accepted that specialist clinicians achieve better outcomes[5,13] and there is evidence also of lower peri-operative mortality in hospitals which deal with large volumes.[38,39]

Chemo-radiotherapy
National guidance recommends chemo-radiotherapy as an alternative to or combined with surgery for selected patients with early stage tumours.[13] Debate also continues surrounding the relative effectiveness of radiotherapy alone versus surgery alone in localised disease[40,41] with the result that clinical opinion determines treatment selection.[35] There have been no published RCTs comparing chemo-radiotherapy alone with surgery alone and the only RCT comparing surgery and radiotherapy was abandoned because of poor recruitment.[42]

Palliative interventions
Once indicated, palliative intervention is directed mainly at relieving dysphagia, which causes not only patient distress but exacerbates the malnutrition that accompanies cancer and terminal illness.[43] Palliation should also aim to minimise hospital stay (particularly in view of a life expectancy of only a few months), relieve pain, eliminate reflux and regurgitation and prevent aspiration.[30] *Ideally* the approach should be rapidly effective, safe and well tolerated and result in tumour bulk reduction and prolongation of survival.

Palliative interventions are numerous.[30,44] The most effective means of achieving palliation is still debated and continues to be a challenge to clinicians.[45,46] A recent narrative review on palliative options suggested that treatment should be individualised with the main options being SEMS, laser or photodynamic therapy, and depending on tumour stage and histopathology, these procedures may be combined with chemotherapy and/or radiotherapy.[30]

Palliative surgery
Until recently surgery was also considered to provide the most effective palliation of dysphagia. However, palliative surgery was associated with a high frequency of morbidity (20-60%) and mortality (10-33%),[44,47] does not improve survival,[48] is associated with deteriorating quality of life despite improved dysphagia[49] and many patients are not candidates for surgery because of underlying medical problems.[50] Therefore palliative surgery is NOT recommended for palliation of dysphagia.[13]

Oesophageal endoprostheses

Endoluminal oesophageal prostheses have been used to relieve dysphagia in patients with oesophageal cancer for 100 years.[30] The semi-rigid plastic Atkinson tube was introduced in 1977[51] and became very popular as it offered the important advantage of endoscopic placement, obviating the need for insertion at laparotomy.[30] Several other varieties of plastic endoprostheses are now in clinical use including the Wilson-Cook,[52,53] Procter Livingstone,[54] and Celestin.[55] However, most clinicians place these devices after peroral dilation of the oesophagus, and both procedures (dilation and placement of semi-rigid devices) are associated with a significant risk of oesophageal perforation.[46] Nowadays only few centres routinely use plastic tubes, especially for patients with stenoses in the straight middle part of the oesophagus.[30]

SEMS were first produced in 1983[56] and have become popular because of their ease of insertion and relative safety. They are placed in the oesophagus in a compressed state within disposable delivery systems. The small external diameter of the delivery mechanism makes insertion easier and reduces the need for dilation of the oesophagus, both of which lessen the risk of perforation. Once deployed, the delivery mechanism is removed and the SEMS expands in the oesophagus. The greater internal diameter (compared to plastic tubes) of the expanded SEMS allows potentially greater relief of dysphagia and the possibility for use as a single therapy for the remainder of the patient's life.[30] The expanded device may also cause pressure necrosis of the tumour in the oesophageal wall.[57] The majority of SEMS are placed under sedation using endoscopy and fluoroscopy.[57]

There are gaps in the cylindrical walls of 'uncovered' SEMS as the metal is arranged in rings or as a wire mesh. Some varieties of SEMS are 'covered' (coated) to prevent ingrowth of tumour into the lumen of the device. Several SEMS are now available on the market with newer and improved designs continuing to emerge. Wallstents (Schneider AG, Bulach, Switzerland) are made of stainless steel and cobalt tubular mesh and may be uncovered, or covered with a polyurethane coat. Gianturco Z stents (Wilson-Cook Europe, Bjaeverskov, Denmark) are similar to Wallstents but possess a zig-zag configuration, are all coated with silicone or polyethylene and have barbs in the middle to prevent migration. The Ultraflex stent (Microinvasive / Boston Scientific Corp., Watertown, USA) is a knitted nitinol wire tube, the gelatin coating of the uncovered form dissolving when contact with oesophageal secretions and body temperature is made. Choice of SEMS seems random among clinicians.[57]

A national survey of a random sample of Acute NHS Trusts in England (Appendix 1) indicated that the vast majority of providers mainly use SEMS rather than plastic tubes for oesophageal stenting. Only 11% of providers used plastic tubes more than occasionally. However, SEMS and their disposable delivery systems are expensive. Additionally, the high rate of repeat interventions for late complications such as tumour ingrowth (uncovered stents), stent displacement (covered stents) and obstruction (due to stent compression or tumour overgrowth at either end)[46] have led some to recommend restricting their use.[43]

Nd-YAG Laser

Laser therapy is a well-established, relatively safe and rapidly effective method of palliation for dysphagia due to oesophageal cancer.[44,58] The Nd-YAG laser is used to destroy (by thermal ablation) lesions obstructing the oesophageal lumen.[30] Laser

therapy can accurately target malignant tissue, minimising damage to surrounding tissue, potentially shortening the recovery period.[59] However recurrent dysphagia is a problem necessitating repeated treatment sessions.[44] Laser therapy has been advocated especially for non-circumferential high tumours growing into the oesophageal lumen in which insertion of stents is difficult.[60]

Chemotherapy
The role of neoadjuvant chemotherapy in patients with localised disease has been discussed above. In patients with advanced disease survival advantages[61-63] and improved quality of life[62,64] have been demonstrated when different chemotherapy regimens were compared. Chemotherapy did not improve survival when compared with supportive care (some patients having had surgery),[65] plastic endoprostheses,[66] no treatment (in patients with plastic endoprostheses) or radiotherapy.[67] National guidance recommends that epirubicin/cisplatin/fluorouracil regimens should be available for patients with advanced oesophageal cancer.[13]

Radiotherapy
High dose palliative external beam radiotherapy (EBRT) compared to interventions that did not include radiotherapy has been shown to significantly improve survival in patients with locally advanced disease[68] but not at lower doses in patients with metastatic disease.[67,69,70] Studies tended to show that the addition of EBRT improved initial relief of dysphagia[67,69,71] and prolonged the time to disease progression[68,69] but reporting of toxicity was not comprehensive and quality of life was not assessed.

A dose-response effect on survival has been demonstrated with intraluminal radiotherapy (brachytherapy) in patients with advanced disease.[72] Dysphagia-free interval (but not survival) was also prolonged in patients who received brachytherapy combined with laser therapy compared to those who received laser therapy alone.[73,74] Dysphagia relief and survival was similar when brachytherapy alone was compared with laser therapy alone.[75] It is recommended that brachytherapy be considered in patients for whom definitive chemo-radiotherapy is not appropriate.[13]

Chemo-radiotherapy
Chemo-radiation compared to radiotherapy alone has been shown to prolong survival in patients with advanced disease in some studies[76,77] but not in others.[78-80]

3.1.7 Prognosis and mortality

Oesophageal cancer, in common with other upper gastro-intestinal (GI) cancers, is associated with late presentation and poor prognosis.[5] Most people with oesophageal cancer survive for only a few months after diagnosis. The overall results of treatment continue to be dismal with an overall one-year survival rate of 27% and five-year survival of 9%.[81] Of those having potentially curative treatment, 40% will not survive the first year and 70% will not survive 5 years.[45]

Oesophageal cancer causes 5% of all cancer deaths in the UK making it the fifth most common cause of death from cancer. In 1997 there were 5,855 deaths in England and Wales from oesophageal cancer.[82] The mortality rate (per 100,000/yr) was 13.6 in men and 8.4 in women.[82]

3.2 Local background

The incidence of oesophageal cancer in the West Midlands* was similar to England & Wales with crude incidence rates per 100,000 of 14.75 in males and 9.95 in females in the year 2000. This corresponds to 390 male cases and 268 female cases. Mortality rates (per 100,000/yr) were also similar to the national average (13.7 in men and 8.9 in women).

3.3 Current service provision

A second survey indicated a similar proportion of West Midlands health providers (19% vs. 21% nationally) still using plastic tubes (Appendix 2). However, West Midlands health providers who still use plastic tubes, use them on an occasional basis only (compared to 11% of English providers who used plastic tubes more than occasionally.)

Analysis of Hospital Episode Statistics (HES) revealed that 20 Acute Trusts in the West Midlands provide prosthesis insertion services for patients with oesophageal cancer (Appendix 3). In 1999/2000 West Midlands residents received 232 stents (range 1-24; median 6.5; 2 inserted by non- West Midlands health providers). This gives a rate of one stent for every 2.8 cases of oesophageal cancer.

4. Effectiveness

4.1 Methods for reviewing effectiveness

4.1.1 Search strategy

The systematic review addressed a focused question with the following elements:

Population- inoperable oesophageal cancer;
Intervention- SEMS;
Comparator- plastic tubes;
Outcomes- any.

A broad comprehensive search strategy was used to identify any potentially relevant literature on SEMS in oesophageal cancer. The MEDLINE, EMBASE and CancerLit electronic databases were searched. Published and unpublished studies were also identified from the Cochrane Library Controlled Clinical Trials Register, National Research Register, Conference abstracts, contacts with experts and citation checking of all articles obtained. Sources were searched from 1980 onwards, as the first SEMS was produced in 1983. No language or age restrictions were applied. The search was completed in August 2002. Appendix 4 lists the combinations of terms used in the search strategy.

4.1.2 Inclusion criteria

Studies were included if the study design was a randomised or pseudo-randomised controlled trial comparing SEMS with plastic tubes. The majority (>50%) of patients

* Year 2000 data provided by the West Midlands Cancer Intelligence Unit

had inoperable oesophageal cancer in included studies. No restrictions were placed on the types of outcome(s) reported. Inclusion and exclusion decisions were made independently by two reviewers.

4.1.3 Data extraction and quality assessment strategy

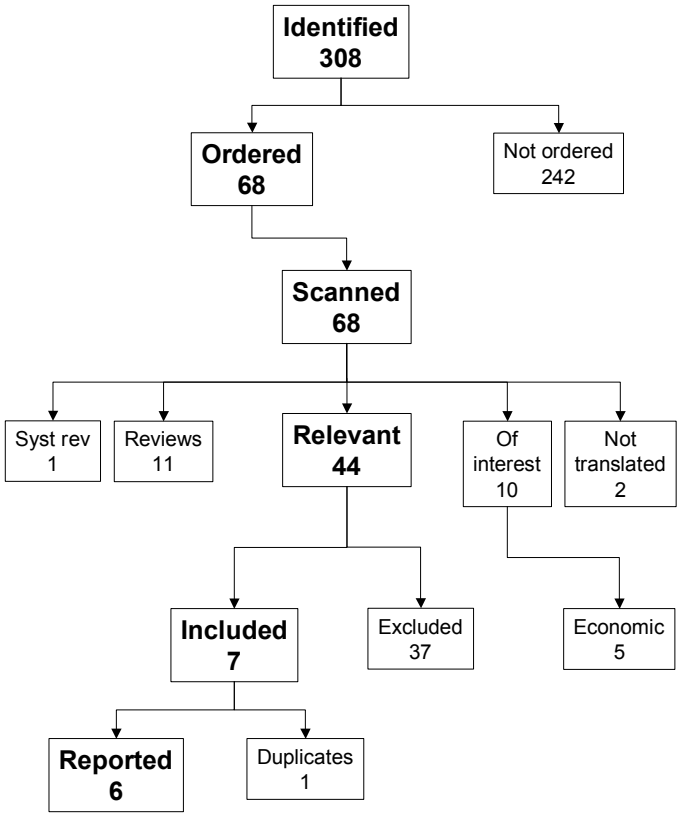
Two reviewers used a standardised data extraction proforma with a quality checklist to independently extract data from and analyse the internal validity of included studies.

4.2 Results

4.2.1 Quantity and quality of available research

Number of studies identified
Figure 1 describes the log of studies identified.

Figure 1 - Outcome log of studies identified



Duplicates
The papers by Alfke and others[87] and Knyrim and others[89] are almost certainly duplicates but attempts to contact the authors to confirm this were unsuccessful. The foreign language duplicate[87] is not described in this report.

Excluded studies
There were 37 studies excluded because they were case series/reports,[90-102] retrospective studies,[103-106] had no SEMS group,[66,105-116] were not randomised/pseudo-randomised,[49,108,111,113,115,117-120] or were not clinical trials.[121,122]

Three RCTs were excluded because the comparators did not include plastic tubes; two (possible duplicates) compared covered SEMS, uncovered SEMS and laser therapy[123,124] and one study compared SEMS to combined therapy with laser and radiation.[125] Two of the foreign language studies were not translated but their English abstracts and year of publication suggest that they are almost certainly not suitable for inclusion.[126,127]

Study characteristics
Table 1 tabulates the characteristics of included studies.

Population
All of the studies except one[84] were conducted in Europe. In all six studies the majority of patients had inoperable oesophageal cancer. Two studies[85,89] included a few patients (<13%) with mediastinal malignancies producing external compression of the oesophagus and three studies included patients with cardial cancers.[83,86,89] Four studies excluded patients with oesophago-respiratory fistulae and proximal tumours,[83,86,88,89] one of these also excluded patients with cardial cancer[88] while two of these four studies also excluded patients based on general health status.[86,89] One study was restricted to only cases with concentric malignancies in which there was still some degree of oesophageal luminal patency[85] while another was limited to patients with squamous cell malignancies.[84]

Intervention
The six studies used a variety of SEMS including uncovered Wallstents,[89] uncovered Ultraflex,[88] covered Wallstents,[83,84] covered modified Gianturco[85] and covered Cook-Z.[86]

Comparator
Different plastic endoprostheses were used including Wilson-Cook,[83,88,89] Procter Livingstone,[84] Atkinson[85] and Celestin.[86]

Quality
The six included studies were of similar quality (Table 2). All of the studies were RCTs but the method of randomisation was not described in one study.[85] They were all small studies, randomised groups ranging in size from 15-38 patients and including a total of 277 patients. Sample size calculation to explain what the studies were powered to detect was not reported in any study; however, one study explained that this was due to the absence of robust clinical data on which to base a sample size estimation.[83]

Table 1 - Characteristics of included studies

Study	Country	Intervention	Median/ Mean age	N	% oesoph/ cardial ca	cervical tumour	% adeno-ca	% squam cell ca	Exclusion criteria	Inclusion criteria
Knyrim[89]	Germany	Uncov'd Wallstent Wilson-Cook	65 69	21 21	90 95		38 43	52 52	Tumour 2cm from UOS Karnofsky score<30 Fistula	Inoperable
DePalma[88]	Italy	Uncov'd Ultraflex Wilson-Cook	68 69	19 20	100 100				Cervical tumour Cardial tumor Fistula	Oesoph thoracic ca Recurrence in inop case
O'Donnell[83]	Scotland	Cov'd Wallstent Wilson-Cook	73 72	25 25	64 (100) 52 (100)		48 56	52 40	Tumour 2cm from UOS No histology confirmation Fistula	Inoperable > 35yr
Sanyika[84]	South Africa	Cov'd Wallstent Procter Livingstone		20 20	100 100			100 100		Inoperable Histology confirmatn
Roseveare[85]	England	Cov'd Gianturco mod Atkinson	71 72	15 16	80 94		60 75	20 19		Inoperable Concentric tumour Diameter stent-gastros
Siersema[86]	Netherlands	Cov'd Cook-Z Celestin	68 65	37 38	70 (100) 74 (100)		68 63	32 34	Tumour 5cm from UOS Unfit for GA Fistula	Inoperable Recurrence post radiatn

Considerable bias in all six studies may have resulted from differential treatment of the randomised groups. SEMS and plastic tubes were the interventions being compared. A greater degree of oesophageal dilation was undertaken in patients randomised to treatment with plastic tubes. Therefore, it could be considered that the studies did not compare SEMS with plastic tubes, but that SEMS with or without minimal oesophageal dilation was being compared to plastic tubes plus extensive oesophageal dilation. This could have resulted in a greater number of dangerous complications (perforation and haemorrhage) that impact on important outcomes (early mortality, survival and duration of hospital stay) among patients with plastic tubes. If routine vigorous oesophageal dilation is an essential part of the procedure for inserting plastic tubes then the groups *were* treated equally apart from the interventions (procedures) being compared. Differential treatment of groups may have occurred also in one study in which five SEMS patients received chemotherapy and one patient randomised to treatment with a plastic tube received radiotherapy.[83] Appendix 5 tabulates the co-interventions employed in the included studies.

No study reported whether those who assessed outcome were unaware of the treatment group to which patients were randomised. However, this lack of observer blinding is unlikely to have resulted in substantial bias since most outcomes (e.g. dysphagia score, survival, duration of hospitalisation and oesophageal perforation) were objective measures not prone to inter-observer variability in measurement.

Only one study[83] reported concealed randomisation, resulting in a JADAD score (a numerical indication of the internal validity) of three for that study compared to scores of two for the other five studies. Randomised groups were not comparable at baseline in two studies.[83,84] Only one study reported blinding of patients.[85] There was differential follow-up of randomised groups in one study.[88] Two studies[85,88] did not employ an 'intention to treat' (ITT) analysis. However it is likely that an ITT analysis of these two studies would have resulted in similar findings because only few patients were not analysed in the groups to which they were randomised. The reporting of results was inadequate in two studies.[84,88] Numbers lost to follow-up were reported or deducible in all six studies. It was not reported who assessed outcome in three studies.[84,88,89]

Table 2 - Quality of included studies

(rand: randomisation; conc: concealed; diff: differential; LTF: loss to follow-up; ITT: intention to treat; inadeq: inadequate; Y: yes; CT: can't tell; onc: oncology; blank = no)

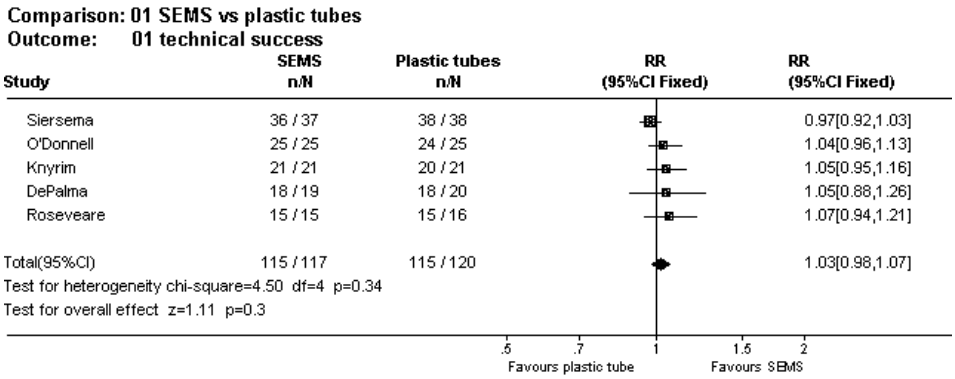
Study	Jadad score	Rand method not stated	Conc rand	Patients blind	Assessors blind	Groups not comp-arable	Diff follow -up	LTF reported	No ITT	Inadeq results	Who assessed outcome
Knyrim et al (1993)	2		CT		CT			Y			CT
DePalma et al (1996)	2		CT		CT		Y	Y	Y	Y	CT
O'Donnell et al (2002)	3		Y		CT	Y		Y			nurse researcher
Sanyika et al (1999)	2		CT		CT	CT		Y		Y	CT
Roseveare et al (1998)	2	Y	CT	Y	CT			Y	Y		nurse specialist
Siersema et al (1998)	2		CT		CT			Y			authors-baseline onc nurse/GP phone

4.2.2 Assessment of effectiveness

Technical success

The technical success (Figure 2) of the intervention was similar for SEMS (95-100%) and plastic tubes (90-100%).

Figure 2 - Technical success of insertion: SEMS vs plastic tubes



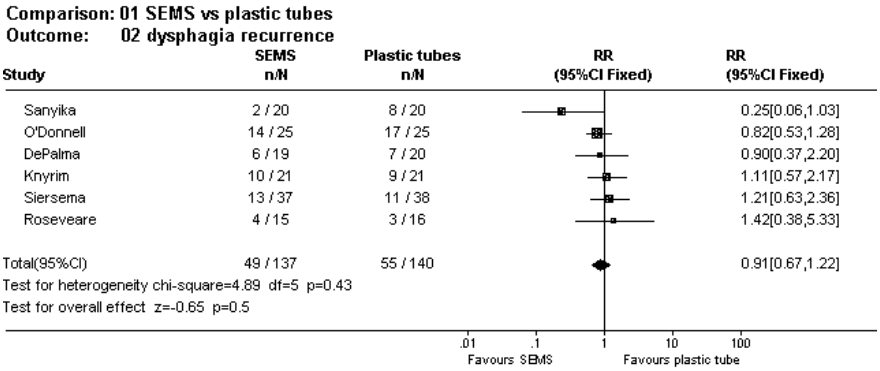
Relief of dysphagia

Only one study showed significantly greater improvement in dysphagia (*P*=0.04) with SEMS compared to plastic tubes (but only at one week and not at six weeks).[85] All SEMS patients in that study had the *SEMS* dilated to 20mm after insertion to ensure adequate expansion of the device.[85] Dilation of SEMS post-insertion was performed in only one other study but only to a diameter of 12mm.[88] In all studies except one[89] there was a trend for greater improvement in dysphagia in patients with SEMS. The internal diameter (ID) of SEMS used ranged from 16-25mm (when expanded maximally) compared to an ID of 12mm for plastic tubes.

Dysphagia recurrence

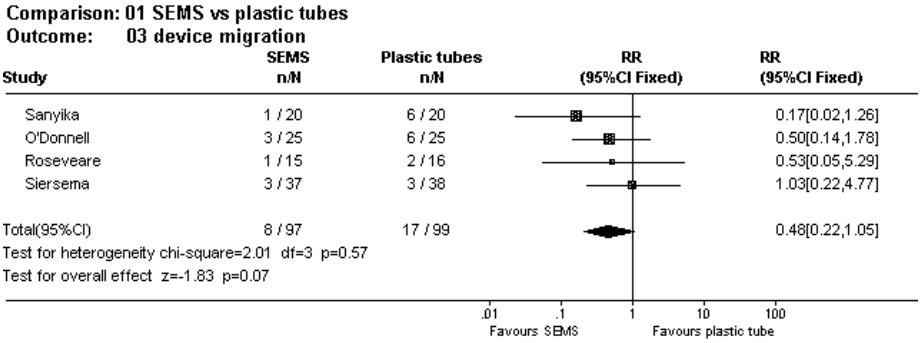
Most studies reported device migration, ingrowth and overgrowth of tumour, food bolus impaction and gastro-respiratory fistula formation as the complications that required re-intervention for recurrence of dysphagia. The frequency of dysphagia recurrence (and life-threatening complications) was reported either as the absolute number of occurrences or as the number of patients affected (or both). There was no significant difference between the groups (Figure 3).

Figure 3 - Dysphagia recurrence: SEMS vs plastic tubes



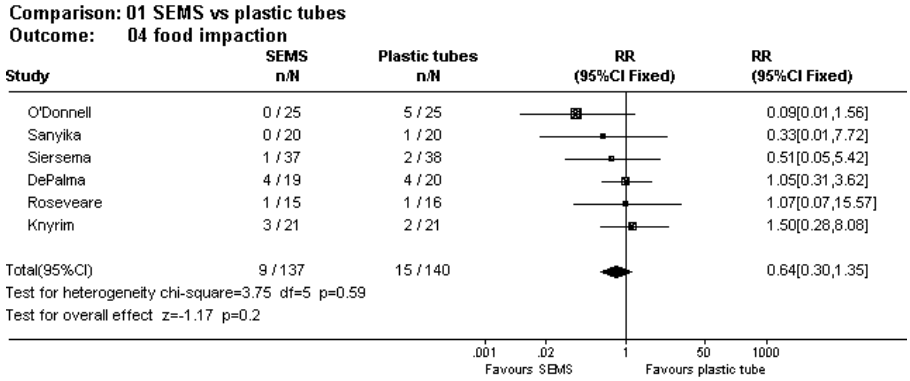
The following frequencies were calculated from the absolute number of occurrences related to the number of patients randomised. This would underestimate the frequencies in studies that reported only the number of patients affected, but between-group comparisons within individual studies would still be valid.

Figure 4 - Device migration: covered SEMS vs plastic tubes



No uncovered SEMS migrated (Figure 4). The frequency of covered SEMS migration (5-35%) tended to be marginally lower than that for plastic tubes (10-30%) in individual studies. Tumour ingrowth did not occur in patients with plastic tubes (but occurred in patients randomised to plastic tubes who received an alternative intervention[83,89]). Only one of the four studies that used covered SEMS reported tumour ingrowth (12%) into the device.[83]

Figure 5 - Food impaction: SEMS vs plastic tubes

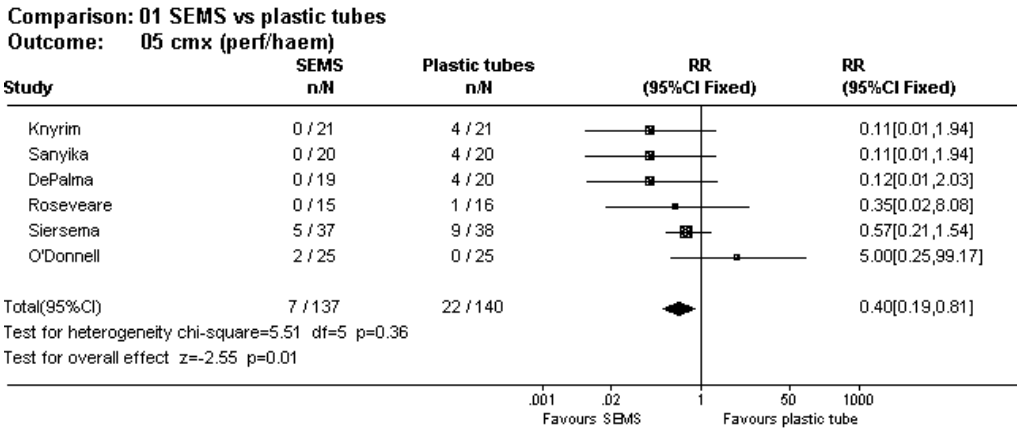


The frequency of tumour ingrowth was 11-14% in groups randomised to uncovered SEMS.[88,89] The frequency of tumour overgrowth (0-24% vs 0-20%) and fistula formation (3-10% vs 0-5%) tended to be marginally higher for SEMS than for plastic tubes in individual studies. Food bolus impaction (Figure 5) occurred with similar frequency among patients with SEMS (0-21%) and plastic tubes (5-20%). One study reported 'other' causes of dysphagia recurrence in one patient (4%) of each group[83] and dysphagia recurred due to fracture of one plastic tube (3%) in another study.[86] When added together, the frequency of all causes of dysphagia recurrence was similar among patients with SEMS and those with plastic tubes.

Procedural complications

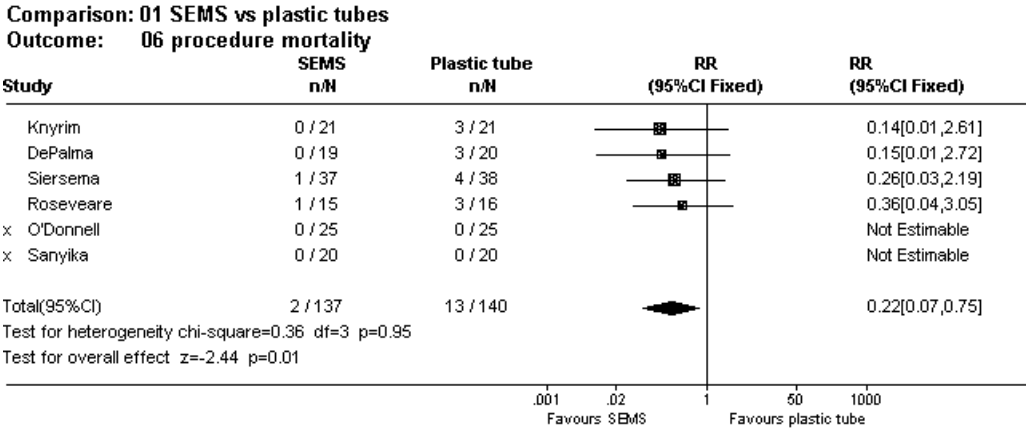
Most studies reported perforation, haemorrhage and pulmonary aspiration as the procedure-related complications that were life-threatening. Figure 6 compares the risk of perforation and haemorrhage (which could also be due to oesophageal dilation) for the two groups.

Figure 6 - Life-threatening procedure-related complications



There was a lower frequency of perforation among patients who received SEMS (0-3%) compared to those given rigid tubes (6-15%) in five of the six studies.[84-86,88,89] In these five studies the oesophagus was dilated to a diameter of only 0-12mm in SEMS patients (in one study the *SEMS* were dilated to 20mm after insertion[85]), compared to a diameter of 17-25mm in patients given rigid tubes. In the only study that reported a higher frequency of perforation among the SEMS group (4 vs 0%) there was less disparity between the degree of oesophageal dilation among SEMS patients (six patients dilated to 12mm) compared to patients with plastic tubes (dilation to a mean diameter of 15mm in most patients).[83]

Figure 7 - Procedure-related mortality: SEMS vs plastic tubes



Haemorrhage also tended to be less common among the SEMS group but the differences were small. The frequency of pulmonary aspiration was similar (0-16% among SEMS vs 0-12% among plastic tubes) but could be related more to anaesthesia and monitoring of patients than to the type of oesophageal endoprosthesis used. Procedure-related mortality (Figure 7) also tended to be lower among patients given SEMS (0-7%) compared to plastic tubes (0-19%) and the difference was reported as statistically significant in one study.[88]

Duration of hospital stay

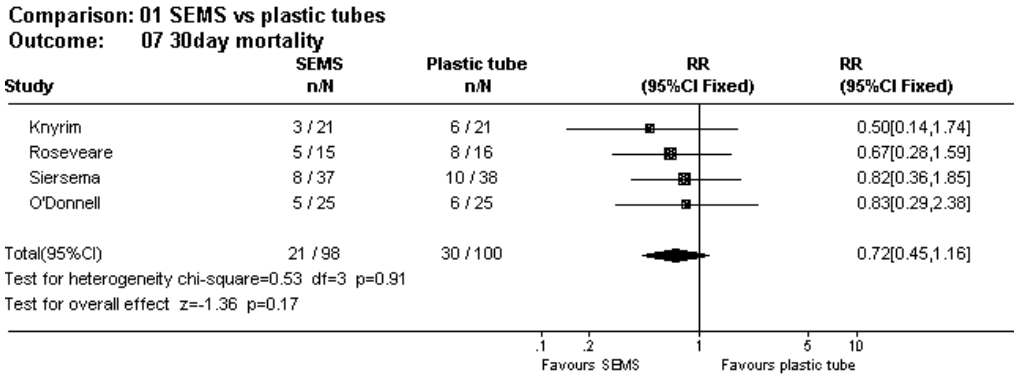
Initial hospitalisation was shorter for SEMS patients in all studies that reported this outcome and ranged from a mean or median of 1-4.3 days for SEMS patients and 3-10 days for patients with plastic tubes.[84-86,89] The difference was statistically significant in two studies.[85,86] Duration of hospitalisation for treatment of complications or dysphagia recurrence was insignificantly shorter for SEMS patients in the two studies that reported this outcome.[83,89] Two studies[85,89] reported total length of hospitalisation and this outcome was shorter for SEMS patients in both studies, achieving statistical significance in one.[89]

Quality of life

Three studies reported either quality of life (QoL)[83,85] or general health status[89] outcomes. One study used a cancer-specific (European Organisation for Research and Treatment of Cancer- EORTC) measure of QoL with an oesophageal cancer-specific module.[83] Another study used the Nottingham Health Profile and Spitzer QoL index.[85]

The Karnofsky score was measured in one trial.[89] No study discovered significant differences between SEMS and plastic tubes.

Figure 8 - 30-day mortality: SEMS vs plastic tubes



Survival / mortality

Survival was reported in five studies.[83,85,86,88,89] The mean or median survival ranged from 69-198 days for SEMS patients and 41-186 days for patients with plastic tubes. Apart from one study,[86] survival tended to be longer among SEMS patients. However, only one study found a statistically significant improvement in survival for SEMS patients.[85] Survival did not appear to be related to serious complications or procedure-related mortality, i.e. studies with the biggest apparent differences in complications and procedure-related mortality had similar survival rates for patients with SEMS and plastic tubes. Thirty-day mortality (Figure 8) was similar among patients with SEMS and those with plastic tubes in the four studies that reported this outcome.[83,85,86,89]

5. Economic analysis

With ever increasing demands on limited resources, information is required not only about the effectiveness of an intervention but also about its efficiency. The *efficiency* of an intervention measures its effect in relation to resources consumed[128] and is therefore a measure of its worth in comparison with an alternative use of the resources. *Economic evaluations*, which use analytical techniques to define resource allocation choices,[129] help determine efficiency. Economic evaluations relate (clinical) outcomes of competing interventions to the resources (cost) they consume.

5.1 Methods for economic analysis

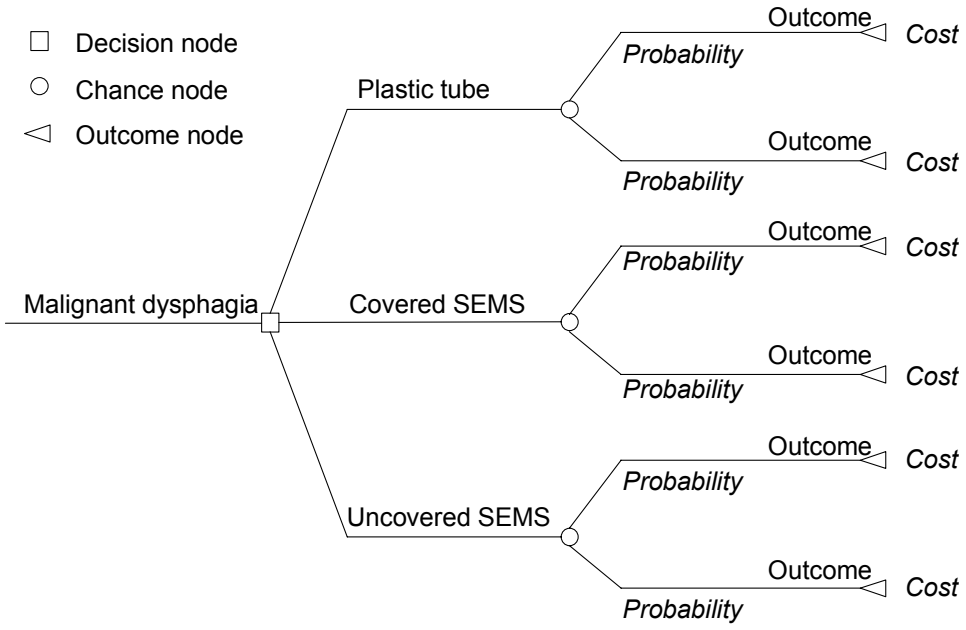
5.1.1 Critical appraisal of published economic evaluations

MEDLINE was searched using an amplified search strategy to identify economic analyses of SEMS in oesophageal cancer. Other web-based reference sources (DARE and NHS EED) were also searched. Identified studies were appraised critically using published guidelines.[130] Economic data from the studies included in the systematic review were also considered.

5.1.2 Decision analysis

Decision analytic frameworks can assist economic evaluations when there is inadequate information on costs and outcomes.[131] Decision analysis is the application of explicit quantitative methods to analyse decisions under conditions of uncertainty, allowing comparison of the expected consequences of pursuing different strategies.[132]

Figure 9 - Decision analysis to model costs



The decision tree was constructed as follows (Figure 9). Decisions and outcomes were represented in order, with earlier events on the left. Alternate intervention pathways followed square nodes, which represented the decision points. Round nodes represented the points at which outcomes occurred by chance (the sum of probabilities of all possible outcomes following a chance node is always one). The utility was measured in terms of the cost of an entire pathway and each terminal outcome node was represented by a triangle. Roll-back calculations (multiplying probabilities and cost) working from terminal nodes to decision nodes (right to left) allowed an evaluation of the cost of individual intervention choices.

Study design

An incremental cost-effectiveness analysis from the viewpoint of the NHS (hospital costs only) was conducted to compare metal with plastic stents for the palliation of malignant dysphagia. The information required for modelling costs and outcomes was obtained from the following sources.

Effectiveness/clinical outcomes

Clinical outcome probabilities and effectiveness data were obtained from the results of the RCTs included in the systematic review.[83-86,88,89] The primary outcomes considered for the cost-effectiveness analysis were survival and relief of dysphagia.

Costs and resources

The resources involved in each decision pathway were determined from a survey of local providers (Appendix 2), from the included studies and from discussions with clinical experts. Costs were obtained from reference publications,[133,134] published studies,[83,135] local providers and medical device manufacturers (Table 5). Costs were reported in UK pounds sterling (£) and inflation-adjusted to reflect 2000/01 prices.[134] Costs and resources were determined for use of Wilson Cook plastic tubes, covered Ultraflex SEMS and uncovered Ultraflex SEMS.

Analysis of results

Costs and outcomes were not discounted because of the short time-scales involved in oesophageal cancer palliation. The published NHS Reference costs were the basis for determining costs for health care involving the use of several types of resource.[133] NHS Reference costs are aggregated costs that represent the full cost for providing a service and include direct, indirect and overhead costs.

One-way sensitivity analysis tested the robustness of conclusions within a range of reasonable uncertainty. Individual outcome probabilities were varied by 10% and costs by 25% or by interquartile range (IQR) for NHS Reference costs[133] to derive a maximum and minimum average cost for each intervention.

It should be noted that sensitivity analysis to determine a maximum reasonable estimate of the average cost of one intervention, resulted in simultaneous increases (albeit smaller) in the estimated costs for the other two interventions since several resources are common to all three interventions. Similarly, the estimated cost of all three interventions decreased when sensitivity analysis was conducted to derive a reasonable minimum average cost of any one of the interventions. Therefore, the

range of incremental cost-effectiveness ratios was *not* determined by comparing minimum cost of one intervention with the maximum cost of the other, but an adjustment was made to account for the simultaneous changes in costs.

5.2 Economic analysis results

5.2.1 Published economic evaluations

Table 3 is a summary of the findings of the six published economic evaluations. Two studies[136,137] reported higher overall costs for plastic tubes although two others[85,89] suggested that plastic tubes become more costly above a threshold cost for hospitalisation, since hospital stay is shorter for patients treated with SEMS.

No study stated explicitly from whose viewpoint the analysis was undertaken although all appear to be from a health service (hospital) perspective. Only one study[85] did not report unit costs and resource quantities separately. The study by O'Donnell et al[83] was the only one to discount costs to reflect long-term use of reusable equipment (e.g. endoscopes) and to report the year to which prices related. The time horizon of all studies except one[84] was long-term, i.e. measuring costs and outcomes for the initial stent placement as well as for re-intervention for treatment of complications or dysphagia recurrence. Three studies[83,85,89] reported the use of sensitivity analysis.

Table 3 - Published economic studies comparing metal and plastic oesophageal stents

(CEA- cost-effectiveness analysis; ICER- incremental cost-effectiveness ratio; LOS- length of hospital stay; long-term- initial placement and follow-up for treatment of complications/dysphagia recurrence)

Study	Type of economic evaluation	Source of effectiveness data	Summary benefit measures	Costs included	Comments/Results
O'Donnell[83]	Costs& outcomes	Single RCT	Survival	Equipment, drugs, staff, overheads, hospital stay	Mean cost significantly > for SEMS only for the first 4 weeks following placement
Sanyika[84]	Costs& outcomes	Single RCT		Hospital stay, theatre time, nursing time, materials	Mean cost > for SEMS
Roseveare[85]	Costs& outcomes	Single RCT		"Materials and procedures"	Mean cost > for SEMS but SEMS cost less if hospital stay >£120/day.
Knyrim[89]	ICER	Single RCT	Premature deaths avoided; LOS	Stent only	ICER $457 per premature death avoided. SEMS cost less if hospital stay >$193/day.
Birch[137]	Costs& outcomes	Retrospective cohort	Dysphagia score, complications	Hospital stay, theatre time, ITU, stents	Median costs > for plastic tubes
Nicholson[136]	CEA	Retrospective cohort	Dysphagia score, survival	Hospital stay, procedures	Mean cost significantly > for plastic tubes. Cost per day palliation and cost per day per improved dysphagia also > for plastic tubes.

5.2.2 Estimation of incremental benefits

Table 4 - Primary outcomes following for incremental benefit estimation

	Study	**Incremental survival advantage of SEMS vs plastic tubes** (days)	**Incremental difference in post-Rx dysphagia score** (when measured)
Covered SEMS	Siersema et al[86]	**-12**	0.1 (4wk)
	O'Donnell et al[83]	45	
	Roseveare et al[85]	55	1 (1wk)
	Sanyika et al[84]		1 (1mth)
Uncovered SEMS	De Palma et al[88]	12	0.5 (immediate)
	Knyrim et al[89]	21	0 (6wk)

Table 4 lists the incremental differences in the primary outcomes used as the summary benefit measures in the economic analysis. Compared to plastic tubes, covered SEMS were associated with an average of 29 days longer survival (range –12 to 55) and uncovered SEMS an average 17 (range 12 to 21) days longer survival. At one week to one month following insertion, covered SEMS were associated with a greater decrease (improvement) in dysphagia score of 0.7 (range 0.1 to 1) compared to plastic tubes. Uncovered SEMS were associated with a greater decrease (improvement) in dysphagia score of 0.25 (range 0 to 0.5) compared to plastic tubes.

5.2.3 Estimation of net costs

Tables 4-7 list the unit costs and resources involved in endoprosthesis insertion and for managing complications and dysphagia recurrence.

Table 5 - Resources and costs for endoprosthesis insertion

Type of resource	Item	Unit cost (£)	Plastic tube	Covered SEMS	Uncov'd SEMS
Bed days	GE ward[134]	£249	1	1	1
Equipment	Wilson-Cook tube[83]	£128	1		
	Cov'd SEMS*	£855		1	
	Uncov'd SEMS*	£705			1
Procedures	Prosthesis insertion[133]	£367	1	1	1
	Contrast study[133]	£111	1	1	1
Total			£855	£1,582	£1,432

* Ultraflex stents; cost information provided by Boston Scientific UK Ltd

Table 6 - Resources and costs for management of non-fatal complications

Type of resource	Item	Unit cost	Non-fatal haemorrhage	Non-fatal perf-oration	Non-fatal aspir-ation
Bed days	GE ward[134]	£249			5
	Surgical ward[134]	£341	2	3	
	HDU[133]	£431	1	2	3
Procedures	CXR[133]	£29		2	2
	Contrast study[133]	£111		1	
Total			£1,113	£2,054	£2,596

Table 7 - Resources and costs for management of fatal complications

Type of resource	Item	Unit cost	Fatal haem-orrhage	Fatal perf-oration	Fatal aspir-ation
Bed days	HDU[133]	£431	2	3	4
Procedures	CXR[133]	£29	1	2	2
Total			£891	£1,351	£1,782

Table 8 - Resources and costs for management of dysphagia recurrence

Type of resource	Item	Unit cost	Diagnostic endoscopy	Therapeutic endoscopy	Dilation	Laser	Plastic tube	Covered SEMS	Uncovered SEMS	Alcohol + needle
Out-patient	Attendance[134]	£134	1	1	1	1	1	1	1	1
Bed days	GE Ward[134]	£249	2	2	2	2	2	2	2	2
Procedures	Contrast study[133]	£111	1	1	1	1	1	1	1	1
	Diagnostic endoscopy[133]	£287	1		1	1	1	1	1	1
	Therapeutic endoscopy[133]	£368		1						
	Dilation[135]	£83			1					
	Laser[135]	£113				1				
	Plastic tube[83]	£128					1			
	Covered SEMS*	£855						1		
	Uncovered SEMS*	£705							1	
	Alcohol + needle**	£25								1
Total cost			£1,030	£1,111	£1,113	£1,143	£1,158	£1,885	£1,735	£1,055

* Ultraflex stents; cost information provided by Boston Scientific UK Ltd

** Cost information provided by endoscopy unit, Birmingham City Hospital

Figures 10-12 are the decision trees outlining the models for the three different endoprostheses. (Haemorrhage and perforation did not occur in any patient receiving uncovered SEMS in both studies[88,89]- Figure 12.) The average cost of using a plastic tube was £1,609, compared to £2,222 for a covered SEMS and £1,967 for an uncovered SEMS.

Figure 10 - Cost of plastic stents

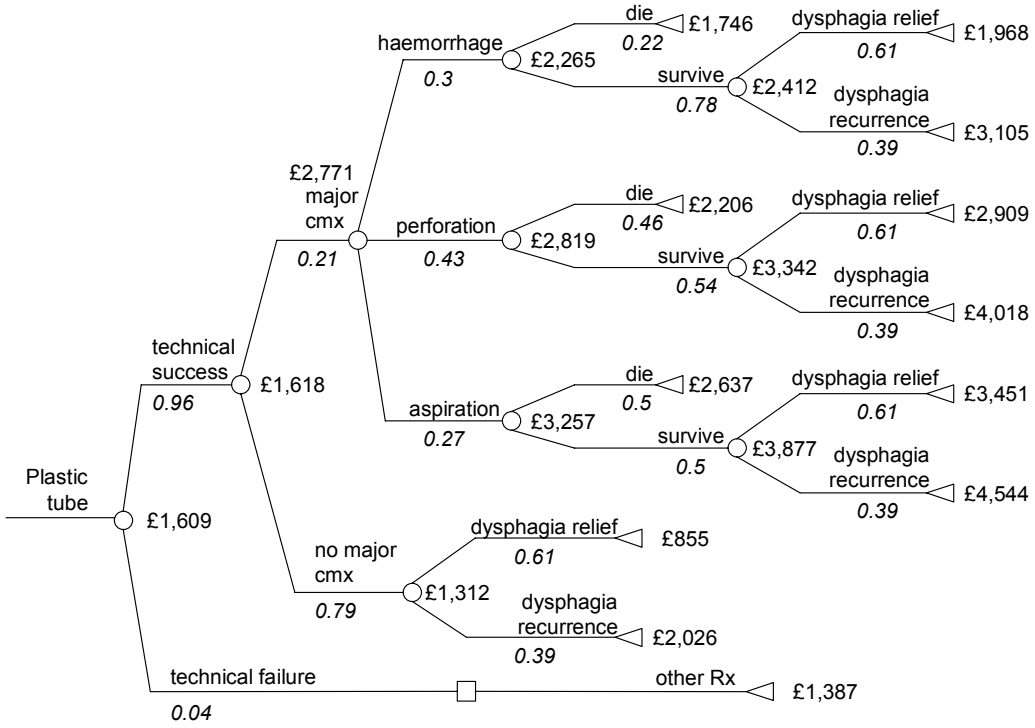


Figure 11 - Cost of covered self-expanding stents

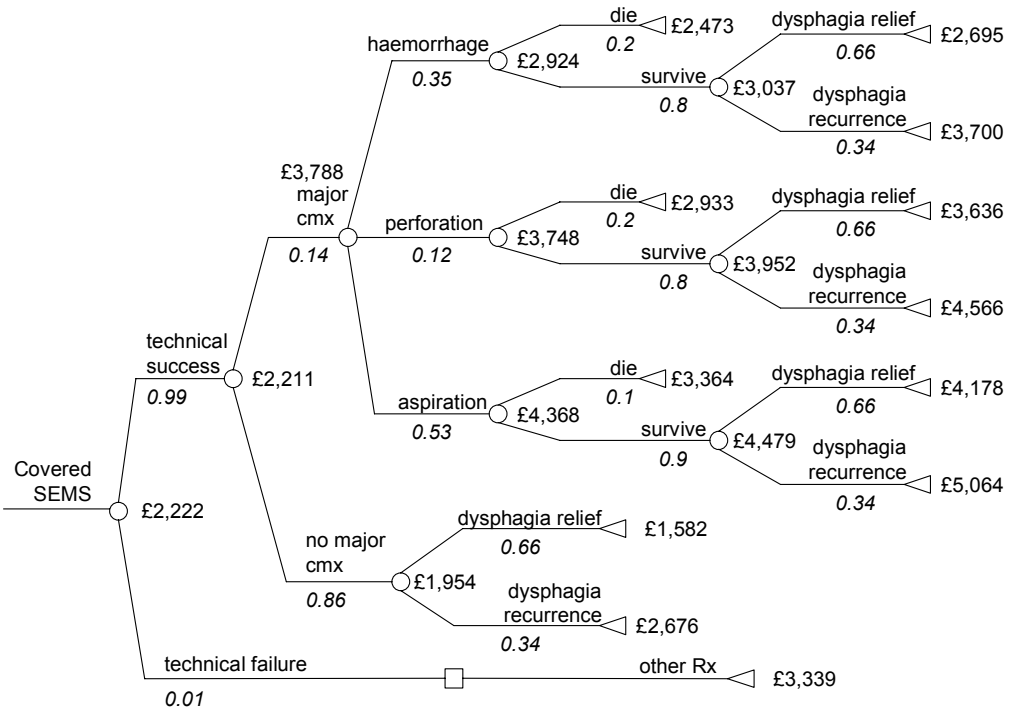
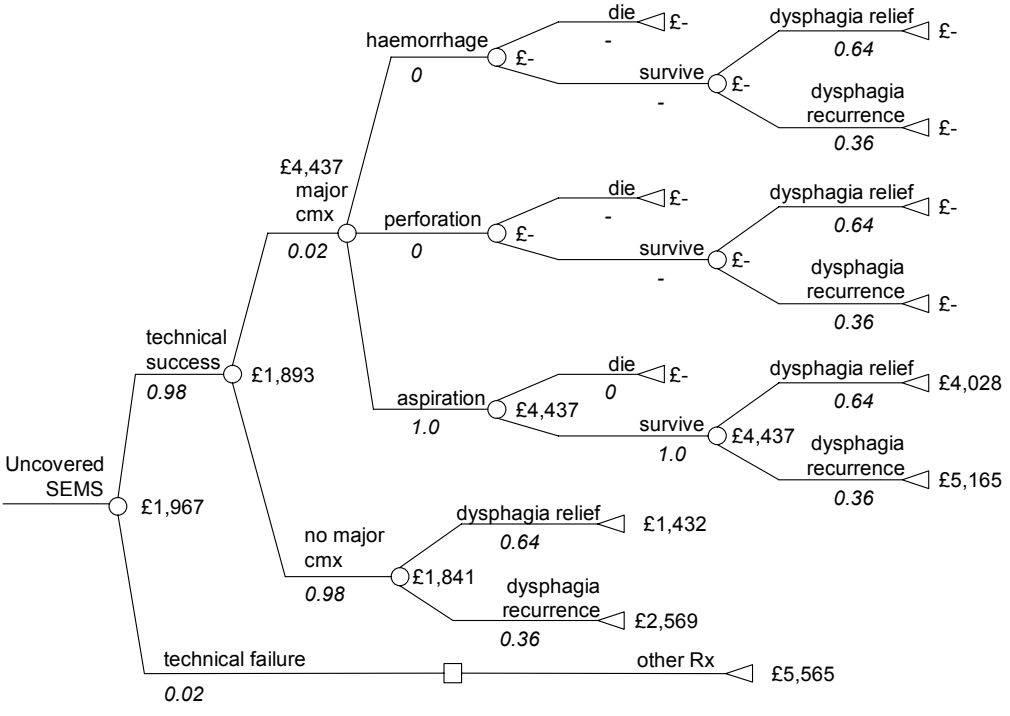


Figure 12 - Cost of uncovered self-expanding stents



5.2.4 Sensitivity analysis

The most important determinants of the average cost of inserting an endoprosthesis were the cost of hospitalisation on a gastroenterology ward, cost of the stent, cost of prosthesis insertion, probability of developing major complications and probability of prolonged dysphagia relief (i.e. of not requiring re-intervention). Other important determinants of average cost were the cost of clinic attendance and cost of each day in the HDU. Probabilities of technical success and of surviving a major complication had little impact.

A reasonable estimation/(range) for the average cost of inserting a plastic tube is £1,610 (1,040-2,250). The corresponding averages for covered SEMS are £2,220 (1,630-3,080) and for uncovered SEMS £1,970 (1,310-2,860).

5.2.5 Incremental cost-effectiveness ratio

Using the above estimates of incremental costs and table 4 for incremental effectiveness, the incremental cost-effectiveness ratios are as follows:

Covered SEMS vs plastic tubes
Survival
Covered SEMS cost on average £610 more and result in *29 days longer survival* compared to plastic tubes or *£21 for every additional day survived* (£7,630 per life-year saved). In the worst case scenario, covered SEMS cost on average £1,670 more and result in 12 days shorter survival. At best, covered SEMS cost £220 less and result in 55 days longer survival than plastic tubes.

Post-intervention dysphagia score
Covered SEMS are associated with a short-term post-treatment dysphagia score of 0.7 lower (better) compared to plastic tubes. This gives a cost of £880 for an added 1-point improvement in dysphagia score. In the worst case scenario the improvement in dysphagia score is only 0.1 and associated with a cost of £16,700 for every additional point improvement in dysphagia score. At best, covered SEMS cost £220 less and result in a 1-point better improvement in dysphagia.

Uncovered SEMS vs plastic tubes
Survival
Uncovered SEMS cost on average £360 more and result in *16 days longer survival* compared to plastic tubes or *£22 for every additional day survived* (£7,920 per life-year saved). In the worst case scenario, uncovered SEMS cost on average £1,440 more for 12 extra days of life or £120 for each additional day survived. At best, uncovered SEMS cost £530 less and result in 21 days longer survival.

Post-intervention dysphagia score
Uncovered SEMS are associated with a short-term post-treatment dysphagia score of 0.25 lower (better) compared to plastic tubes. This gives a cost of £1,430 for an added 1-point improvement in dysphagia score. In the worst case scenario there is no additional improvement in dysphagia score with uncovered SEMS but they cost

£1,440 more. At best uncovered SEMS are associated with a 0.5 point better improvement in dysphagia score associated with £530 lower cost.

6. Implications for the West Midlands NHS

Oesophageal endoprostheses are used in 230 patients for the palliation of dysphagia due to oesophageal cancer in the West Midlands each year. Use of SEMS would incur additional costs of £140,000 each year for the West Midlands secondary health care sector, but this would be associated with an average of one month longer survival. Uncertainty in the data gives a range of £125,000 in savings for 8 weeks longer survival, to £385,000 extra cost for no survival advantage (2 weeks shorter survival).

7. Discussion

7.1 Main results

7.1.1 Efficacy of SEMS

Six small RCTs compared SEMS with plastic tubes.

In patients with inoperable oesophageal (excluding proximal tumours) and cardial cancer, compared to plastic endoprostheses SEMS were associated with, on average (range)-
Marginally improved survival of 24 days longer (-12 to 55);
Marginally lower 30-day mortality of 7% less (-4 to 20%);
Similar quality of life scores;
Marginally better *initial* improvement in dysphagia scores of 0.5 greater decrease (0 to 1);
Similar rates of dysphagia recurrence (10-56 vs 19-68%);
Significantly lower rates of perforation and haemorrhage of 11% less (-8 to 20%);
Significantly lower procedure-related mortality of 9% less (0 to 14%);
Shorter initial (mean/median 1-4 vs 3-10 days) and total (5-8 vs 12-12.5 days) duration of hospitalisation and
Similar technical success rates (95-100 vs 90-100%);

All six included studies were prone to bias from a lack of observer blinding and differential treatment (oesophageal dilation) of randomised groups. There was considerable clinical heterogeneity (choice of SEMS, choice of plastic tubes and patient selection) among the studies.

7.1.2 Cost-effectiveness of SEMS

The average cost of inserting a plastic tube is about £1,610. The corresponding averages for covered SEMS are £2,220 and for uncovered SEMS £1,970.

Covered SEMS cost on average £21 more for every additional day survived and about £880 for an added 1-point improvement in dysphagia score. Uncovered SEMS cost on

average £22 more for every additional day survived and about £1,430 for an added 1-point improvement in dysphagia score.

The use of SEMS costs the West Midlands secondary health care sector an extra £140,000 each year for 230 patients to live for an average of one month longer.

7.2 Limitations

7.2.1 Bias

The included studies were prone to bias that could explain partially the marginal benefits of SEMS over plastic tubes. Lack of observer blinding could have biased the measuring and reporting of outcomes. There was also the possibility of differential treatment, with a greater degree of oesophageal dilation in patients randomised to plastic tubes. Therefore, it could be considered that the studies did not compare SEMS with plastic tubes, but that SEMS with or without minimal oesophageal dilation was being compared to plastic tubes plus extensive oesophageal dilation. Oesophageal dilation can result in dangerous complications (perforation and haemorrhage) that impact on important outcomes (early mortality, survival and duration of hospital stay). If routine vigorous oesophageal dilation is an essential part of the procedure for inserting plastic tubes then the groups *were* treated equally apart from the interventions (procedures) being compared.

7.2.2 Heterogeneity

The meta-analysis results should be interpreted with caution because of the considerable clinical heterogeneity among studies. Limitations of the cost-effectiveness analysis include the use of aggregated costs. However, to disaggregate the resources involved would have been very difficult for such a complex decision tree.

7.3 Outcomes

7.3.1 Relief of dysphagia

Greater dysphagia relief may have been expected with SEMS because of their larger internal diameters (ID 16-25mm vs. 12mm for plastic tubes). All *SEMS* were dilated to 20mm after insertion to ensure adequate expansion of the device in the only study reporting significantly greater improvement in dysphagia.[85] Only 12mm diameter dilation (the same ID as plastic tubes) of *SEMS* was achieved in the only other study in which metal stents were dilated post-insertion.[88]

7.3.2 Procedural complications

In the five studies that reported lower perforation rates for SEMS the *oesophagus* was dilated to a diameter of only 0-12mm in SEMS patients, compared to a diameter of 17-25mm in patients given rigid tubes.[84-86,88,89] In the only study reporting a higher frequency of perforation among the SEMS group, there was less disparity between the degree of oesophageal dilation among SEMS patients (≤12mm) compared to patients with plastic tubes (15mm mean).[83] The lower frequency of haemorrhage and

procedure-related mortality among the SEMS group may be due also to differential oesophageal dilation.

Pulmonary aspiration (which was similar in both groups) is probably related more to anaesthesia and monitoring of patients than to the type of oesophageal endoprosthesis used.

7.3.3 Duration of hospital stay

Since procedure-related complications were lower among SEMS patients in most studies, it is unsurprising that initial hospitalisation was also shorter.[84-86,89]

7.3.4 Quality of life (QoL)

Quality of life (QoL) is the outcome used increasingly nowadays to evaluate the quality, effectiveness, and efficiency of health care.[138] This is especially important in malignant disease where treatment may be associated with prolonged survival but considerably worse QoL. A reliable and valid questionnaire (EORTC QLQ-C30) for international use in evaluating QoL in cancer patients has been developed[139] and an oesophageal cancer-specific module added (QLQ-OES 24).[140]

Difficulties with measuring QoL, and attributing it to health and health care, arise partly because of individuals' vastly different expectations;[138] i.e. individuals with the same clinical condition and functional ability may report different QoL because of different expectations of health.

Since it is the commonest complaint in oesophageal cancer, dysphagia should represent an important determinant of QoL[141] and patients confirm that this is so.[142] However, treatments such as surgery can improve dysphagia while QoL deteriorates.[49] Nevertheless dysphagia is correlated with psychological well-being and other QoL indicators after palliative intervention.[49]

No study found significant differences in QoL or general health status[83,85,89] but only one study used the oesophageal cancer-specific questionnaire.[83]

7.3.5 Survival / mortality

Survival did not appear to be related to serious complications or procedure-related mortality, i.e. studies with the biggest apparent differences in complications and procedure-related mortality had similar survival rates for patients with SEMS and plastic tubes.[83,85,86,88,89]

7.3.6 Local SEMS provision

The marginal benefits of SEMS reported in clinical trials may not reflect the substantial benefits due to their ease of insertion[30,57] that occurs in everyday use. Unpublished data from a comprehensive 5-year audit (1992-96) of West Midlands cases revealed 23 perforations from 524 plastic tubes (4.4%) and none from 157 SEMS (personal communication, EW Gillison). However a smaller retrospective analysis suggested that ease of insertion does not always translate into beneficial effects.[143]

7.3.7 Cost-effectiveness

Six published economic analyses comparing SEMS with plastic tubes were found. Four reported greater average costs for SEMS.[83-85,89] This was consistent with the findings of the present study. Two studies reported that plastic tubes were overall more expensive due to the costs of managing and the longer hospitalisation resulting from procedure-related complications.[136,137]

These differences may be explained by contrasting methods of inserting stents and confirming their position, with resulting differences in resources used. Even if the same resources were used, different costing methodology may arrive at dissimilar results. Studies varied also in resources that were considered; e.g. in one study the only cost considered was that of the stent alone.[89]

8. Conclusions

There is fair evidence that SEMS offer marginal benefits in prolonging survival, reducing hospitalisation and major complications, and improving dysphagia relief compared to plastic tubes in patients with inoperable oesophageal cancer. These benefits are associated with a small additional cost.

The disadvantages of plastic tubes could possibly be reduced if less oesophageal dilation was employed during their insertion. Conversely, ensuring optimal expansion of SEMS post-insertion and appropriate dietary advice to patients could result in greater and more prolonged benefits in dysphagia relief.

The ease of insertion of SEMS may result in greater clinical and economic benefits in everyday practice than those observed in clinical trials.

8. APPENDICES

Appendix 1 - National survey of SEMS provision

Methods

A computer-generated random sample of 10% of the 274 Acute NHS Trusts in England yielded 35 Trusts of which 13 were excluded because they were either Community or Ambulance Trusts. A short questionnaire was then used in a telephone survey. The nurse-in-charge at the time of contacting the endoscopy unit was the respondent surveyed.

Questionnaire

Results

The response rate was 86%. Of the responders, 21% used plastic as well as metal stents but only two (11%) units used plastic tubes more than occasionally.

Appendix 2 - Survey of SEMS provision in the West Midlands

Aims

The aims of this survey were twofold; (1) to determine resources used in endoprosthesis insertion to inform the economic analysis (Chapter 4) and (2) to assess the effectiveness of local SEMS provision to inform a wider evaluation of SEMS provision. Only the results that are relevant to this review are presented.

Methods

A questionnaire was piloted with the help of local clinicians. A letter was sent to the Nurse-in-Charge of 18 endoscopy units in the region asking for their assistance in the survey. (Two provider units were inadvertently omitted from the sampling frame.) Two weeks later the telephone survey was conducted.

Questionnaire

Results

The response rate was 94%. All providers used SEMS but only 19% used plastic tubes as well.

The procedure for inserting SEMS varied considerably. In 25% of units they were done as day-cases; under general anaesthesia in 13%; in the radiology department in 67% (in the endoscopy unit in 20% and in theatres in 13%); and by the gastroenterologist in 88% (by surgeons in 31% and radiologists in 13%).

Adequate position was confirmed by fluoroscopy (44%), contrast studies (31%), plain X-ray (13%) or endoscopy (6%). Dietary advice was provided in most cases (81%) from a variety of sources (nurse specialist 19%; diet sheet 19%; dietician 25%; nutrition team 6%; registered nurse 13%).

Patients were followed-up routinely as an out-patient in 19% or had open access to the clinic (13%), nurse specialist (19%) or endoscopy unit (13%).

Appendix 3 - Stents received by West Midlands residents

Oesophageal endoprostheses inserted by West Midlands providers for West Midlands patients in 1999/2000

Acute NHS Trust	**Number of stents**
Burton Hospitals	1
Hereford Hospitals	3
Alexandra Healthcare	4
Kidderminster Healthcare	4
Sandwell Healthcare	4
Birmingham Heartlands & Solihull	5
South Warwickshire General Hospitals	5
The Princess Royal Hospital	6
The Royal Wolverhampton Hospitals	6
George Eliot Hospital	7
Good Hope Hospital	10
Worcestershire Acute Hospitals	12
Walsall Hospitals	17
City Hospital	19
Mid Staffordshire General Hospitals	19
Royal Shrewsbury Hospitals	20
Walsgrave Hospitals	20
Dudley Group of Hospitals	22
North Staffordshire Hospital	22
University Hospital Birmingham	24
Total	230

Data source: West Midlands Safe Haven HES Pilot, Public Health Institute, University of Birmingham
(West Midlands residents received a total of 232 stents, i.e. 2 stents were provided outside of the West Midlands.)

Appendix 4 - Search strategy

The key elements of the strategy were as follows (see main report for further details):

Electronic searches of MEDLINE (Ovid Biomed)

The following combination of terms were used-

1 esophag$.mp
oesophag$.mp
exp Esophagus/
or/1-3
cancer$.mp
carcin$.mp
neoplasm$.mp
malignan$.mp
tumour$.mp
tumor$.mp
"squamous cell".mp
adenocarcinoma$.mp
exp Neoplasms/
or/5-13
4 and 14
exp Esophageal Neoplasms/
15 or 16
stent$.mp
SEMS.mp
prosthes$.mp
endoprosthes$.mp
intubat$.mp
exp Stents/
exp Intubation/
exp Intubation, Gastrointestinal/
exp Prostheses and Implants/
or/18-26
17 and 27
exp Randomized Controlled Trials/
exp Random Allocation/
exp Clinical Trials/
exp Double-Blind Method/
exp Placebos/
exp Cross-Over Studies/
exp Research Design/
exp Comparative Study/
randomized controlled trial.pt
controlled clinical trial.pt
clinical trial.pt
multicenter study.pt
(clini$ adj trial$).mp
(control$ adj (trial$ or stud$)).mp
((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp
placebo$.mp

random$.mp
or/29-45
28 and 46
limit 47 to publication date 1980-2001

Electronic searches of EMBASE (BIDS Ovid)
The following combination of terms were used-
esophag$.mp
oesophag$.mp
exp Esophagus/
or/1-3
cancer$.mp
carcin$.mp
neoplasm$.mp
malignan$.mp
tumour$.mp
tumor$.mp
"squamous cell".mp
adenocarcinoma$.mp
exp Malignant neoplastic disease/
or/5-13
4 and 14
exp Esophagus tumor/
exp Esophagus cancer/
or/15-17
stent$.mp
SEMS.mp
prosthes$.mp
endoprosthes$.mp
intubat$.mp
exp Stent/
exp Intubation/
exp Esophagus intubation/
exp Prosthesis/
exp Esophagus prosthesis/
or/19-28
18 and 29
exp Randomized controlled trial/
exp randomization/
exp Clinical trial/
exp Double blind procedure/
exp Placebo/
exp Crossover procedure/
exp Controlled study/
exp Intermethod comparison/
exp Comparative study/
"randomized controlled trial".mp
"randomized controlled trials".mp
"randomised controlled trial".mp
"randomised controlled trials".mp

“clinical trial”.mp
“clinical trials”.mp
“multicenter study”.mp
“multicenter studies”.mp
“multicentre study”.mp
“multicentre studies”.mp
(clini$ adj trial$).mp
(control$ adj (trial$ OR stud$)).mp
((singl$ OR doubl$ OR trebl$ OR tripl$) adj (blind$ OR mask$)).mp
placebo$.mp
random$.mp
or/31-54
30 and 55
limit 56 to publication date 1980-2001

Electronic searches of CancerLit (Ovid Biomed)
The following combination of terms were used-
esophag$.mp
oesophag$.mp
exp Esophagus/
or/1-3
stent$.mp
SEMS.mp
prosthes$.mp
endoprosthes$.mp
intubat$.mp
exp Stents/
exp Intubation/
exp Intubation, Gastrointestinal/
exp Prostheses and Implants/
or/5-13
4 and 14
exp Randomized Controlled Trials/
exp Random Allocation/
exp Clinical Trials/
exp Double-Blind Method/
exp Placebos/
exp Cross-Over Studies/
exp Research Design/
exp Comparative Study/
“randomized controlled trial”.mp
“randomized controlled trials”.mp
“randomised controlled trial”.mp
“randomised controlled trials”.mp
controlled clinical trial.pt
controlled clinical trials.sh
clinical trials.sh
controls.mp
multicenter study.pt
(clini$ adj trial$).mp

(control$ adj (trial$ or stud$)).mp
((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp
placebo$.mp
random$.mp
or/16-37
15 and 38
limit 39 to publication date 1980-2001

Appendix 5 - Co-interventions

Study	Interventions (n =)	Dilation	Placement	Other
Knyrim[89]	Uncov'd SEMS (n = 21) Plastic tube (n = 21)	10mm balloon- 14pts 20mm balloon; serial prn	sedation GA	Laser- 3pts
DePalma[88]	Uncov'd SEMS (n = 19) Plastic tube (n = 20)	10-12 mm; 12mm post-insertn 18-20 mm	diazepam5-10 GA- 60%	
O'Donnell[83]	Cov'd SEMS (n = 25) Plastic tube (n = 25)	12mm balloon- 6pts 14-19mm (mean15)- 18pts	diamorph5 + midaz 2-10 GA- 4/23; others- diamorph5 + midaz 2-10	ChemoRx-5 Radiation- 1
Sanyika[84]	Cov'd SEMS (n = 20) Plastic tube (n = 20)	12mm balloon 25mm bougie	midaz 5-10 + LA GA	
Roseveare[85]	Cov'd SEMS (n = 15) Plastic tube (n = 16)	to gastroscope OD prn; + 20mm post-insertn 51Fr Keymed	diazepam + peth diazepam + peth	
Siersema[86]	Cov'd SEMS (n = 37) Plastic tube (n = 38)	8mm 17.2mm Keymed	midaz GA	

Appendix 6 - Assumptions in respect of costs and benefits

(The term 'intervention' is used to describe the type of oesophageal endoprosthesis used, i.e. plastic tube, covered SEMS or uncovered SEMS.)

An average of the incremental benefit from individual studies is used in the cost-effectiveness ratio calculation.

The costs of all relevant and important resources used in procedures, admissions and clinic attendances have been included in the summary costs provided by the Department of Health[133] and by the Personal Social Services Research Unit.[134] Therefore, the only other costs considered were for resources that may not have been included in the summary costs of a particular procedure/admission/attendance or those that would be different for each intervention.

The average cost of stent insertion (Table 5) includes the cost of: the device, one day on a gastroenterology ward, oesophageal prosthesis insertion and one contrast study.

The average cost of managing non-fatal complications is the same for all three interventions and outlined as in Table 6; e.g. for non-fatal haemorrhage the average cost includes the cost of: two days on a surgical ward and one day in HDU.

The average cost of managing fatal complications is the same for all three interventions and outlined as in Table 7; e.g. for fatal haemorrhage the average cost includes the cost of: two days in HDU and one chest X-ray.

The average cost of a therapeutic approach for managing dysphagia recurrence due to a particular problem (e.g. food bolus impaction) is the same for all three interventions and outlined as in Table 8. For example, the average cost of 'therapeutic endoscopy' used to manage dysphagia recurrence due to food bolus impaction, includes the cost of: one outpatient attendance, two days on a gastroenterology ward, one contrast study and one therapeutic endoscopy.

The probability of dysphagia recurrence in patients receiving a particular intervention is the same for those who do not develop major complications as for those who survive any major complication.

Dysphagia recurrence in patients with plastic tubes is managed as follows.
Tube migration: SEMS (40%), therapeutic endoscopy (40%), laser (20%);
Food bolus impaction: therapeutic endoscopy (100%);
Tumour overgrowth: alcohol injection (80%), laser (20%);
Fistula formation: SEMS (50%), diagnostic endoscopy (50%).

Dysphagia recurrence in patients with covered SEMS is managed as follows.
Tube migration: uncovered SEMS (60%), oesophageal dilation (40%);
Food bolus impaction: therapeutic endoscopy (100%);
Tumour overgrowth: alcohol injection (70%), SEMS (20%), laser (10%);
Fistula formation: plastic tube (80%), diagnostic endoscopy (20%).

Dysphagia recurrence in patients with uncovered SEMS is managed as follows.
Tumour ingrowth: laser (100%);
Food bolus impaction: therapeutic endoscopy (100%);
Tumour overgrowth: alcohol injection (70%), SEMS (20%), laser (10%);
Fistula formation: plastic tube (80%), diagnostic endoscopy (20%).

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