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Abstract

A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer

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Objectives: To compare whether treatment with self-expanding metal stents (SEMS) is more cost-effective than treatment with conventional modalities in patients with inoperable oesophageal cancer. Quality of life effects were also considered.

Design: A multicentre pragmatic, randomised controlled trial with health economic analysis.

Setting: Seven NHS hospitals selected to represent a cross-section of UK hospitals in terms of facilities and staffing.

Participants: All patients attending the centres with oesophageal cancer deemed unsuitable for surgery were assessed for inclusion in the main trial; 217 patients were randomised. A health state utilities substudy was also performed in 71 patients who had previously received curative surgery for oesophageal cancer.

Interventions: Eligible patients were randomised to one of four treatment groups within two study arms. Assessments were performed at enrolment, 1 week following treatment and thereafter at 6-weekly intervals until death, with prospective data collection on complications and survival. Structured interviews to elicit patient preferences to health states and treatments were performed in a substudy.

Main outcome measures: Dysphagia grade and quality of life were examined at 6 weeks. Survival, resources consumed from randomisation to death and quality-adjusted life-years were also considered.

Results: There was no difference in cost or effectiveness between SEMS and non-SEMS therapies, and 18-mm SEMS had equal effectiveness to, but less associated pain than, 24-mm SEMS. Rigid intubation was associated with a worse quality of swallowing and increased late morbidity. Bipolar electrocoagulation and ethanol tumour necrosis were poor in primary palliation. A survival advantage was found for non-stent therapies, but there was a significant delay to treatment. The length of stay accounts for the majority of the cost to the NHS. Patients were found to have distinct individual treatment preferences.

Conclusions: It was suggested that rigid tubes and 24-mm SEMS should no longer be recommended and bipolar electrocoagulation and ethanol tumour necrosis should not be used for primary palliation. The choice in palliation would between non-stent and 18-mm SEMS treatments, with non-stent therapies being made more available and accessible to reduce delay. A multidisciplinary team approach to palliation is also suggested. A randomised controlled clinical trial of 18-mm SEMS versus non-stent therapies with survival and quality of life end-points would be helpful, as would an audit of palliative patient admissions to determine the reasons and need for inpatient hospital care, with a view to implementing cycle-associated change to reduce inpatient stay. A study of delays in palliative radiotherapy treatment is also suggested, with a view to implementing cycle-associated change to reduce waiting time.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Dysphagia Difficulty in swallowing.

Functional success When treatment is accompanied by the ability of the patient to sustain oral nutrition post-treatment.

Laser Light amplification by the stimulated emission of radiation.

Oesophagus The gullet.

Operability Whether or not a patient is able to undergo surgery with a reasonable expectation of cure.

Palliation Relief of symptoms without cure.

Quality-adjusted life-year A measure combining level of health (in terms of impact on quality of life) with duration, standardised to a 1-year period.

Quality of life The functional effect of an illness and consequent therapy upon a patient, as perceived by a patient.

Resectability Whether or not the local tumour can be physically removed from the patient.

Stage The anatomical spread of disease.

Technical success The ability to restore luminal patency without complication or failure, generally equating to the ability to pass an 11-mm diameter endoscope through the stricture after treatment.

Utility A measure of the value of health states.

List of abbreviations

5-FU	5-fluorouracil
ACA	adenocarcinoma
ANOVA	analysis of variance
APC	argon plasma coagulation
AUGIS	Association of Upper Gastrointestinal Surgeons
BICAP®	bipolar electrocoagulation
BMI	body mass index
C/E	cost–effectiveness ratio
CCA	cost-consequences analysis
CEA	cost-effectiveness analysis
CHSR	Centre for Health Services Research
CI	confidence interval
CT	computed tomography
CU	cost–utility ratio

continued

List of abbreviations *continued*

CUA	cost–utility analysis
EBRT	external beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
ETN	ethanol-induced tumour necrosis
EUS	endoscopic ultrasound
KPS	Karnofsky Performance Scale
MREC	Multicentre Research and Ethics Committee
MS	mean square
MSE	mean square error
ND	no data
Nd:YAG	neodymium–yttrium aluminium garnet
NOGU	Northern Oesophago-Gastric Unit
ns	not significant
PDT	photodynamic therapy
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SD	standard deviation
SE	standard error
SEMS	self-expanding metal stent(s)
SG	standard gamble
SS	sum of squares
TNM	tumour, node, metastases
TTO	time trade-off

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Inoperable oesophageal cancer is a devastating diagnosis. Without treatment, swallowing deteriorates with dramatic effects on quality of life. There is no evidence for using one dysphagia-relieving palliative treatment over another. Self-expanding metal stents (SEMS) may be most effective, but are expensive and the NHS burden of palliation is escalating. A prospective, randomised controlled trial (RCT) is essential for informed, cost-effective treatment choice.

Objectives

The primary objective of this study was to compare whether treatment with SEMS is more cost-effective than treatment with conventional modalities in patients with inoperable oesophageal cancer.

The secondary objectives were also included as part of the study. The first was to to determine whether metal stents provide a better quality of swallowing, require fewer follow-up interventions and provide a greater number of quality-adjusted life-years. The second was to determine quality of life effects associated with all treatment and health outcomes.

Methods

Design

A multicentre pragmatic RCT with health economic analysis.

Setting

Seven NHS hospitals were selected to represent a cross-section of UK hospitals in terms of facilities and staffing.

Subjects

All patients attending the centres with oesophageal cancer deemed unsuitable for surgery were assessed for inclusion in the main trial; 217 patients were randomised. A health state utilities substudy was also performed in 71 patients who had previously received curative surgery for oesophageal cancer.

Interventions

Eligible patients were randomised to one of four treatment groups within two study arms. Assessments were performed by research nurses at enrolment, 1 week following treatment and thereafter at 6-weekly intervals until death, with prospective data collection on complications and survival. Structured interviews to elicit patient preferences to health states and treatments were performed in a substudy, using one of two randomly assigned techniques.

Main outcome measures

The main outcome measures were: dysphagia grade at 6 weeks; quality of life at 6 weeks; survival; resources consumed from randomisation to death; and quality-adjusted life-years.

Results

It was found that there was no difference in cost or effectiveness between SEMS and non-SEMS therapies. It was also found that the 18-mm SEMS had equal effectiveness to, but less associated pain than, 24-mm SEMS. Rigid intubation was associated with a worse quality of swallowing and increased late morbidity. Bipolar electrocoagulation and ethanol-induced tumour necrosis were found to be poor in primary palliation. A survival advantage for non-stent therapies was evident, but with a significant delay to treatment. The length of hospital stay accounts for the majority of the cost to the NHS. Patients were found also to have distinct individual treatment preferences.

Conclusions

It was concluded that rigid tubes and 24-mm SEMS should no longer be recommended. Similarly, bipolar electrocoagulation and ethanol-induced tumour necrosis should not be used for primary palliation.

Implications for healthcare

It is suggested that the choice in palliation should be between non-stent and 18-mm SEMS treatments, and that non-stent therapies should be made more available and accessible to reduce delay. A

multidisciplinary team approach to palliation may be appropriate, with consideration also being given to length of stay in order to reduce the NHS burden of palliation, with due regard to quality of life and costs.

Recommendations for further research

A randomised controlled clinical trial of 18-mm SEMS versus non-stent therapies considering survival and quality of life end-points would be valuable. An audit of palliative patient admissions is also suggested in order to determine the reasons and need for inpatient hospital care, with a view to implementing cycle-associated change to reduce inpatient stay. Delay in palliative radiotherapy treatment should also be studied, with a view to implementing cycle-associated change to reduce waiting time.

Chapter 1
Background

Summary

A randomised controlled trial (RCT) of the cost-effectiveness of palliative therapies in patients with inoperable oesophageal cancer was carried out.

Oesophageal cancer

The growth of fleshy, obstructing lesions in the oesophagus leading to swallowing difficulties, emaciation and eventual death was described in Biblical times.[1] Despite dramatic recent changes in epidemiology and the development of lower risk surgery for a minority of patients, not many facts have changed since this description, with oesophageal cancer remaining a devastating diagnosis and a significant clinical problem. The majority of patients have inoperable disease and without treatment the ability to swallow deteriorates rapidly with a dramatic effect on quality of life.[2–5] For these patients it is vitally important to palliate and improve their symptoms. There has been a recent, alarming increase in the incidence of the disease and, together with an ageing population, this has led to a significant increase in the NHS burden of resources consumed by palliative treatments.

The pressure for quicker, more effective palliation has culminated in a proliferation of treatments, with clinicians and healthcare managers facing choices between costly, new treatments that are alleged to be more effective and efficient than previous therapies. The evidence for using one treatment over another is based almost entirely on observational non-comparative studies, none of which has demonstrated convincing superiority of any of these treatments. The number and diversity of the available therapies reflect this. Attempts to perform good quality, randomised, clinical trials have been hampered by design flaws that have weakened their findings. This deficiency was recognised by the HTA arm of NHS research and development, primarily as a result of the escalating cost of palliation. As such, a prospective RCT is essential for informing treatment choice in the future.

Pathology

Many types of malignancy can occur within the oesophagus, but all are rare in comparison with squamous cell carcinoma (SCC), derived from the lining epithelium, and adenocarcinoma (ACA), thought to arise from mucosal and submucosal glandular tissue which is located predominantly at the oesophagogastric junction. The principles of palliation apply to them equally, with individual variations in modalities and techniques for tumour characteristics and site.

Incidence

In 1990 cancer of the oesophagus was the eighth most common form of malignancy worldwide. It accounted for over 300,000 new cases, 4% of all new cancers, and was the sixth most frequent cause of cancer mortality.[6] However, there has been a recent increase in the incidence of tumours of the lower third of the oesophagus, specifically the oesophagogastric junction, in the populations of Western Europe and North America.[7,8] These are of the ACA subtype and such has been the increase in numbers of cases that this has overtaken the previously more common SCC as the predominant histological oesophageal tumour subtype.[9,10] Population-based studies suggest that the increase in incidence is in the order of 4–10% per year, with the trend most marked in white, male populations.[11,12] The mortality from oesophageal cancer in the UK is now the highest in Europe, with an incidence of 6.6 per 100,000 population for all subtypes in 1995 (*Figure 1*), making it the eighth most common tumour in the UK.[13,14] In Scotland the current incidence of oesophageal ACA appears to be approaching 15 per 100,000 population, an increase of 139.5% from 1977 to 1996.[8,15] Despite the likelihood of this figure being considerably higher 5 years on, at the time of writing, the disease is of surprisingly low public and media profile.

Demographics

Oesophageal cancer is a disease of the elderly, with almost negligible incidence in people less than 40 years old, but rising gradually thereafter to be most prevalent in the seventh and eighth decades of life. There is evidence that in high-

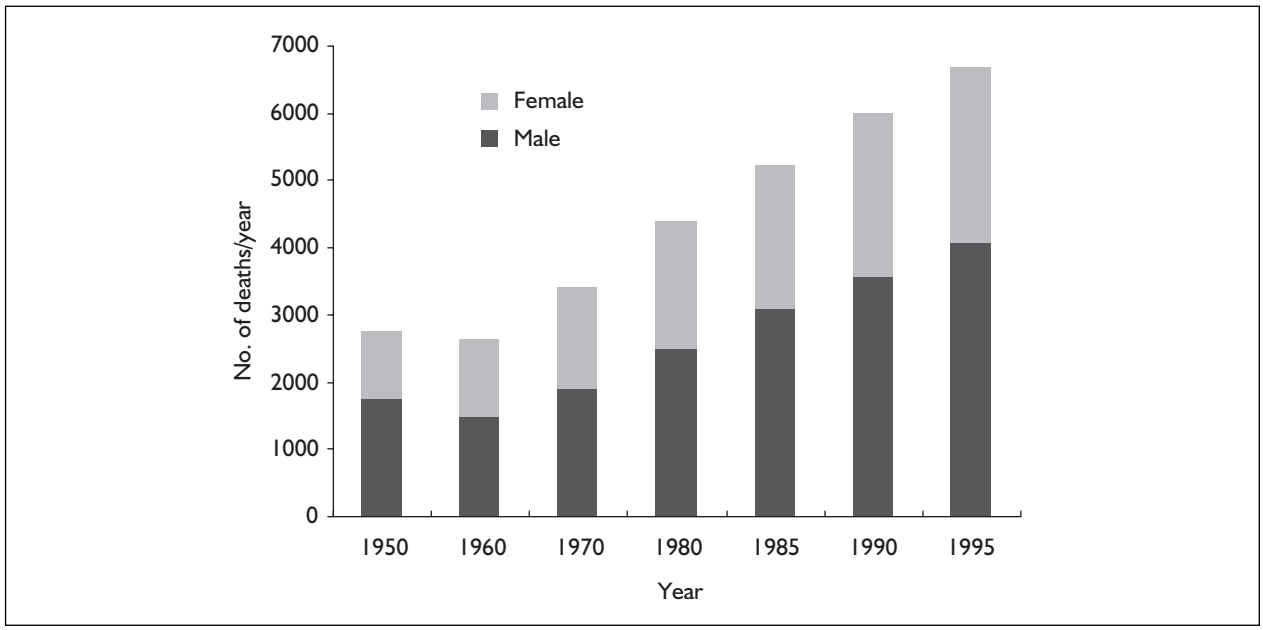

FIGURE 1 *Number of deaths/year in the UK from cancer of the oesophagus (World Health Organization)*

prevalence areas the age at diagnosis may be falling and there is a tendency for cohorts of people born recently to be subject to a higher incidence than previous population cohorts.[16] It will take years for the effects of these changes to become apparent in the population as a whole. Men are predominantly affected, with a male to female ratio of 2:1; however, the recent increase in ACA is more marked in women.[17] The incidence varies among differing ethnic groups with SCC four to five times more common in black populations and ACA showing a predominance in whites.[18]

Aetiology

The cause of the recent increase in incidence of oesophageal ACA is unknown, although some aetiological factors have been established. These differ between the histological subtypes.

Squamous cell carcinoma

Diet, cigarette smoking and alcohol are the main aetiological risk factors for SCC of the oesophagus, which noticeably occurs in poverty-stricken populations. In well-nourished, non-drinking, non-smoking white Western men, SCC of the oesophagus is virtually non-existent.[19]

Adenocarcinoma

In contrast, oesophageal ACA is a disease of prosperity, with the most dramatic changes in incidence occurring in affluent Western countries. The most important and significant risk factor is that of gastro-oesophageal reflux. In 1999, a large-scale, case-controlled, epidemiological study in Sweden confirmed this association, finding that the more frequent, severe and longer lasting the reflux symptoms, the greater the risk.[20] A high body mass index (BMI) also has a significant, proportional association with oesophageal ACA, independent from reflux.[20]

Clinical presentation

The predominant symptom of oesophageal cancer is progressive dysphagia, with 80–90% of patients having some degree of difficulty in swallowing.[21,22] However, initial symptoms may be vague, varying from an uneasy sensation on swallowing or mild dyspepsia to a total inability to swallow food and fluids, including saliva. As a result, many patients delay attending their GP. In a review of 360 patients treated in one centre, 73% had symptoms for greater than 6 months before diagnosis.[23] Nor is the degree of dysphagia always proportional to the degree of luminal obstruction, with highly symptomatic small and asymptomatic large tumours.[24] As a whole, dysphagia occurs once there has been at least a 60% reduction in lumen diameter, implying fairly advanced disease before the onset of alarming symptoms.[21,25] Dysphagia worsens with disease progression, and weight loss develops with the subsequent change in dietary intake. A small number of patients present with symptoms of locally advanced disease, such as a persistent cough due to aspiration or a fistula, a hoarse voice due to recurrent laryngeal nerve involvement or back pain due to mediastinal invasion, and some present with features of distant

spread, such as general malaise, fatigue, anorexia and right upper quadrant abdominal pain due to liver metastases, dizziness or confusion due to cerebral secondaries, dyspnoea due to a malignant pleural effusion or lung metastases or bone pain with bony metastases.

Physical signs are similarly vague until the late stages of disease. Weight loss is the most frequent physical feature, but dehydration may be noticeable earlier. In later stages of the disease there may again be signs associated with locally advanced disease or distant metastases, such as palpable supraclavicular cervical lymphadenopathy, ascites, jaundice or lung signs.

Advanced disease

The terms 'operability' and 'resectability' are often quoted and used interchangeably, but poorly understood. Operability is defined as whether or not a patient is able to undergo surgery with a reasonable expectation of cure, thereby implying that they possess the necessary physical fitness to withstand the procedure and do not have tumour spread to distant sites so that removal would not constitute a curative treatment. In contrast, resectability is whether or not the local tumour can be physically removed from the patient. As such, patients may have resectable disease but be inoperable owing to poor fitness or distant metastases or, conversely, have operable but unresectable disease because of local invasion, so that removal would not be possible without damaging vital structures.

Unresectable disease

Distant metastatic spread:

- to distant organs (e.g. liver, lung, bone, cerebral)
- to distant nodal sites (e.g. coeliac axis, para-aortic or cervical nodal stations).

Locally advanced:

- local vital structure invasion (e.g. the aorta or airways)
- (large mediastinal nodal burden).

Delay to diagnosis

Five-year survival is in the order of 20% for those with operable disease who undergo a curative intent resection, but many patients have advanced disease at time of presentation so that surgery is not possible.[2] This can often be blamed on a delay in diagnosis due to the vague nature of symptoms. Martin and colleagues demonstrated that the median delay to histological diagnosis from first symptoms was 17.3 weeks and that advanced disease was associated with longer delays; even the presence of dramatic and alarming symptoms such as dysphagia did not expedite diagnosis.[26] Wayman and colleagues demonstrated that four-fifths of this delay was due to the failure of the patient to attend their GP and a reluctance by the GP to refer to hospital.[27]

Referral

In a review of 1201 oesophageal surgery papers by Muller and colleagues, the mean resectability rate was 21%, with variations between centres reflecting referral patterns and case-mix.[2] In a specialist surgical centre, the referral pattern and attitude of staff dictate that more patients are likely to have exploration; in the Leeds surgical unit, 42% of referred patients had a surgical exploration, with 79% undergoing resection (i.e. a resectability rate of 33%).[28] Conversely, many potential surgical candidates may not be referred for surgery by their GP; instead, they receive palliative support from their community care team or are referred for assessment by medical colleagues who err away from surgery owing to the perceived poor prognosis. As a result, 30% of worthwhile surgical candidates are denied the chance of a potentially curative operation.[28]

Staging

Once the diagnosis has been made, patients undergo staging to assess operability and resectability, so that a choice can be made between curative surgery and palliative treatment. Three elements are considered:

- stage of disease
- physical fitness
- patient preference.

The Association of Upper Gastrointestinal Surgeons (AUGIS), a national body of UK surgeons with a specific interest in oesophagogastric malignancies, in conjunction with the Department of Health, has produced clinical guidelines aiming towards a national consensus on the staging and selection of patients for surgery or palliation (http://www.dh.gov.uk/cancer).[29]

Stage of disease

Tumour growth occurs both circumferentially and longitudinally, and once the cancer has breached the muscularis propria and the surrounding adventitia, curative resection becomes less likely and more difficult because of the intimate anatomical

relationships within the mediastinum. Early lymphatic spread is common and is characteristic of the disease, with local spread occurring via submucosal lymphatics with occasional skipping of nodal stations to more distant sites.[30] Haematogenous spread via submucosal veins most commonly affects capillary filter beds present in the liver, lung and bones. Cure is not deemed possible if there is evidence of distant spread or if there is locally advanced disease. These situations constitute an absolute indication for palliation. Increasingly, a large nodal tumour burden is viewed as representing unresectable disease and, as staging modalities such as endoscopic ultrasound improve the accuracy of assessing nodal stage, this will assume greater importance.[30]

Staging investigations include clinical examination, blood tests, radiography, endoscopy, spiral computed tomography (CT) and endoscopic ultrasound (EUS). Further investigations may be used to focus on specific areas (e.g. bronchoscopy, laparoscopy or isotope bone scanning). This battery of tests ensures that the minimum number of patients is understaged or overstaged, so that few will undergo unnecessary surgery and few will be denied the potential chance of cure.

Physical fitness

Oesophagectomy is a huge physical insult and patients have to withstand both the radical nature of the surgery and the physiological trauma of one-lung anaesthesia. The majority of patients are elderly, and although physical age itself does not preclude the surgery, physiological fitness declines with advancing age and it is more likely that elderly patients have co-morbid disease. As such, careful assessment of fitness is required to limit operative mortality and morbidity. In particular, it is important to assess cardiorespiratory status, and this forms part of the staging process. History and clinical examination are crude indicators of physical status, but many centres routinely perform full blood count, serum electrolytes, arterial blood gases, an ECG, pulmonary function testing and a simple exercise test. Occasionally, a formal anaesthetic, cardiological or respiratory opinion may be required and sought. Even palliative treatments and the sedation that they entail can be too demanding for some patients to tolerate, and this must be borne in mind, especially as the disease progresses.

Patient preference

There is an increasing awareness of health and healthcare in the public domain, with information freely available to patients and relatives on the Internet. Some patients may choose minimal medical involvement, whereas others may demand care at any cost, even specifying their preferred treatment modality. Informed personal choice is an individual's prerogative and has to be respected within the bounds of evidence-based practice.

Selection for treatment

It is not always possible to provide clear-cut evidence of inoperability or unresectability, and as the staging process becomes more complex it can also become less clear. It is therefore necessary to look objectively at the selection of patients for surgery or palliation and in this regard the multidisciplinary meeting is a useful forum for discussion of cases. These are still relatively uncommon in surgical practice and yet judicious patient selection can influence surgical and palliative outcomes.[31,32] Hennessy demonstrated this in a study where patients were only excluded from surgery if they had extremely advanced disease or were severely unwell, resulting in unacceptable in-hospital mortality of 22%.[33,34] As there are no agreed standards for staging, selection, surgery, palliation or even the collection of patient data, comparisons between unit outcomes are impossible to make. This will remain the case until guidelines are followed, preoperative scoring systems (such as p-POSSUM) are more commonly used and national data collection is implemented.[35]

Palliation

Surgery is the mainstay of curative treatment, but despite more patients, more sophisticated staging modalities and a reduction in operative mortality, resection rates are broadly similar today to those of the pre-1980 studies, with only a minority of patients being suitable for resection.[34,36] Cure is possible, but survival is not the only parameter of success and an oesophagectomy has dramatic effects on quality of life.[37] Blazeby and colleagues demonstrated in a prospective study that patients who did not survive for more than 2 years after curative surgery never regained their preoperative quality of life.[38] Since only 54% of surgical patients survive for more than 2 years, this implies that many patients would not and do not benefit from the rigours of radical surgery.[36,39] As a result, the majority of patients require treatments to alleviate symptoms, but that do not cure. These are termed palliative treatments, derived from the Latin term *palliare*, to cloak, and may be used as primary therapy or after failure of curative surgery. Palliation is not just 'hiding' the disease, however, and the WHO currently defines it as "the active, total care of a person whose condition is not responsive to curative treatment".

In oesophageal cancer palliation predominantly entails the relief of dysphagia without cure. Difficulty in swallowing, dysphagia, is the single, most burdensome symptom of oesophageal cancer, with dramatic effects on daily functioning, social interaction and quality of life. Quantity of life can also be affected, as dysphagia leads to potentially fatal complications such as aspiration pneumonia. Dysphagia affects at least 70% of patients presenting with oesophageal cancer and is almost invariably present in advanced cases. Since inoperable oesophageal cancer patients rarely survive beyond 12 months, with a median survival of 4–6 months, rapid and lasting restoration of swallowing is the primary objective of a palliative therapy programme.[40] Relief of oesophageal obstruction has been shown to improve and maintain quality of life and may lead to a serendipitous survival advantage through improved nutrition and the prevention of early death. Dysphagia is quantifiable and an important outcome of palliation, and as such is frequently used to assess effectiveness of treatment.

Treatments to improve swallowing fall into two groups: those that debulk the tumour through direct destruction of intraluminal disease, thereby recanalising the oesophageal lumen, and those that mechanically replace the lumen, such as by placement of a rigid tube through the tumoral stenosis. Even within these groups there is a wide variety and diversity of treatments, reflecting the number of factors involved in the decision to palliate, such as patient, tumour and local healthcare issues. The disease affects a heterogeneous population and as such there are considerable disparities in age, nutritional status, co-morbid conditions and psychosocial status, especially with the increasing numbers of younger patients being seen. As a consequence, where a one-off treatment may be appropriate for some patients, repeated therapy may be more suitable for others. Similarly, younger patients may tolerate a more aggressive treatment with a potential survival benefit at the expense of physiological, psychological and social disruption, whereas an elderly, frail individual would not. Tumour factors vary in terms of histology, site, consistency of tumour tissue and stage of disease, and a treatment suitable for a soft, polypoid carcinoma close to the oesophagogastric junction may be less suitable for a hard tumour placed more proximally. Local, organisational factors may also play a role in the choice of palliative therapy, such as cost, hospital accessibility and treatment availability. Finally, patient and clinician preference must be taken into account as preconceptions can affect outcomes. Since every patient is unique in these regards it appears unlikely that one treatment would benefit all, hence the profusion of available therapies.

The increase in incidence of oesophageal cancer together with an ageing population means that the burden of palliation to the NHS has increased appreciably. The pressure for quicker, more effective palliation has further stimulated the proliferation of available treatments. Medical device companies are keen to take advantage of this expanding market. Consequently, clinicians and healthcare managers face a barrage of costly new treatments that are allegedly more effective and efficient than previous therapies. The number and diversity of the available therapies reflect not only the complexity of the disease, but also the lack of a distinct advantage of one therapy over another. After consideration of the patient, tumour and local factors, clinicians are faced with a choice between treatments that have not been adequately compared in studies. Studies of outcomes and complication rates tend to be observational and non-comparative. When comparative studies have been performed, none has demonstrated that any treatment is convincingly superior to any other. Randomised trials are scarce and design flaws have weakened the findings of those that have been carried out. As such, clinicians have poor and frequently anecdotal evidence to weigh up and accrue to their own personal experience. The primary outcome of almost all studies to date is dysphagia relief, based on the assumption that quality of life is directly proportional to dysphagia grade.[41] However, Blazeby and colleagues demonstrated that dysphagia accounted for only 15–20% of the variance in quality of life, and other domains such as pain and physical functioning may play a more important role.[41] Travelling to hospital and inpatient stays are demoralising and costly in an elderly patient group, so that reintervention rates as a result of functional treatment failure and associated complications are also important outcomes. Morbidity of treatment has been investigated by previous research studies, but variation in technique can account for many complications and as such standardised treatment protocols are the only way to evaluate therapies accurately. As such, research questions persist in oesophageal cancer palliation in terms of cost-effectiveness, quality of life issues, morbidity and quality of swallowing associated with treatments.

Review of the current forms of palliative treatment

The available evidence for clinicians to choose between therapies is poor. Most studies are retrospective, observational and non-comparative, reporting technical success with associated morbidity and mortality, rather than functional success, quality of life and other quantifiable outcome measures. Often patients receive more than one therapy to achieve palliation in these studies and as a result outcomes are not based on a single modality of treatment. The disparity of outcomes and lack of constants, with various techniques being used at various doses for various stages of various histology cancers, makes it difficult even to compare between studies on a historical basis. Palliation is not attractive to clinicians and grant-holding bodies, so that most oesophageal cancer research tends to be based on potential cure, despite the majority of oesophageal cancer patients ultimately requiring palliation. As such, few of the therapies have been subjected to comparative testing or randomised controlled clinical trials. The best evidence to date is presented in this review.

Debulking techniques

Laser

Initial enthusiasm for laser treatment as a stand-alone palliative therapy has waned since it is time consuming and repeated transportation to hospital is demanding for elderly patients.[42] However, laser treatment is useful for temporary dysphagia relief before either curative surgery or definitive palliation and in secondary palliation: managing recurrence after surgery or overgrowth and ingrowth of tumour tissue in patients with oesophageal stents. Laser therapy also illustrates the principles of tumour ablation that are used in increasingly popular, newer techniques such as argon beam photocoagulation.

Laser is an acronym, standing for light amplification by the stimulated emission of radiation. A directional, monochromatic beam of electromagnetic radiation is targeted against tumour tissue and absorption of energy leads to thermal necrosis and vaporisation, the degree of absorption being dependent on the wavelength, laser–tissue distance, duration of exposure, power output, aim and focus, and tissue colour. For oesophageal cancer the lasing medium is neodymium–yttrium aluminium garnet (Nd:YAG) crystal, which produces a coherent beam of 1064-nm wavelength, infrared light, and is often paired with a visible red xenon laser aiming beam. Treatment is given as endoscopic sessions with time between to allow necrotic tissue to separate. The Nd:YAG laser causes 2–3 mm of necrosis, leaving an eschar that can be cleared by lavage or abrasion 48–72 hours later. The tumour is usually ablated from distal to proximal (retrograde) after passing through the lesion, 20–30% requiring predilatation to allow the endoscope to pass. Although associated with considerable morbidity, the pretreatment dilatation may account more for the rapid relief of dysphagia than the actual laser treatment.[43] Antegrade treatment can be used if it is not possible to pass the endoscope or guidewire, but carries a higher risk of perforation as the view is restricted by thermally induced oedema.[44]

Technique

Treatments are performed under intravenous sedation. A Teflon-coated, quartz-tipped fibre is passed down the biopsy channel of a standard endoscope to convey the laser light. Coaxial carbon dioxide or nitrogen dioxide is used to cool the quartz tip and to help to clear generated smoke together with endoscopic suction. Multiple 0.5–1-second pulses are administered, 5–10 mm from the tumour surface. A sapphire crystal tip attachment can be used to allow contact so the laser can be used like a hot knife. This uses lower energy outputs, thus limiting the depth of thermal damage and, in theory, reducing the perforation risk; however, in one randomised study, Radford and colleagues demonstrated no differences or advantages for contact over non-contact laser therapy with respect to number of treatment sessions, relief of dysphagia or occurrence of complications.[45]

Technical success for laser treatment is consistently over 90% (*Table 1*), but there is a steep learning curve and the treatment is highly operator dependent. Laser therapy is most effective for straight, short (<5 cm), midoesophageal, exophytic, slow-growing tumours.[52] Conversely, it is best avoided for proximal, long or angulated tumours, gastro-oesophageal junction cancers and firm, scirrous disease with a large submucosal component.[53] Angulated and long tumours reblock easily because of a diminished gravity effect in an aperistaltic oesophagus, and proximal tumours close to the cricopharyngeus are difficult to treat as manoeuvring the endoscope for application of treatment is uncomfortable; this is an area where a general anaesthetic and rigid endoscopy may play a role. However, laser is generally well tolerated under sedation. Retrosternal discomfort is rarely a problem unless one area of tumour has received a large amount of

TABLE 1 *Effectiveness of laser therapy for palliation*

Reference	Patients	Technical success	Functional success	Mortality	Morbidity
Fleischer and Kessler, 1983[42]	60	100%	80%	0/60	5%
Krasner *et al.*, 1987[46]	76	93.4%	77%	5%	5.3%
Shmueli *et al.*, 1992[47]	86	89.6%	79%	4%	12%
Bourke *et al.*, 1996[48]	70	96%	70%	1.4%	4.4%
Savage *et al.*, 1997[49]	211	90%	80.6%	9%	15.2%
Abdel-Wahab *et al.*, 1998[50]	104	93%	93%	5.8%	4.8%
Norberto *et al.*,1999[51]	174	ND	82%	0/174	0/174
Mason, 1996[43]	189	ND	91%	ND	ND
Overall	970	93.7%	80.3%	3.6%	6.7%

ND, no data were available in the study.

treatment leading to heat transmission through the mediastinum, which may explain the poor response of submucosal disease.[54]

In observational studies over 80% of patients are palliated successfully with laser treatment, with most patients able to swallow semi-solid or solid food. However, 25% of patients will only ever achieve partial relief of dysphagia with laser treatment and 10% appear not to improve at all.[46] Early failure of treatment may be technical or due to rapid tumour regrowth, extrinsic compression or perforation, and many patients gain no palliative benefit owing to unanticipated early death. Some patients have persistent swallowing difficulties despite the clearance of luminal disease, an enigma peculiar to debulking therapies which may result from motility disturbances secondary to muscle infiltration by tumour, similar to that seen in tumour-related pseudoachalasia.[55–57] In addition, 'tumour anorexia' may develop, where poor dietary intake postpalliation results from a lack of confidence in the ability to swallow foods that were previously troublesome.[56,57] As such, the most important predictor of postlaser dysphagia relief is often prelaser anorexia. This may be the case with all palliative therapies.

Usually between two and four sessions are required to achieve initial dysphagia palliation, with further treatment every 4–8 weeks following this.[43,51] With a median survival of 5 months the average patient will require 4 days' worth of treatment, the majority (86%) of which can be performed on an outpatient basis.[48] Up to 60–70% of patients develop recurrence of dysphagia requiring further treatment or an additional other treatment such as intubation, but the remaining 30–40% maintain satisfactory swallowing until death, with laser treatment alone.[4,46,47]

Complications and drawbacks

Perforation accounts for the majority of significant early morbidity and occurs in 1–6% of treatments.[4,42,48,50,53,57] It is most common following antegrade treatment or when pretreatment dilatation has been used to facilitate retrograde tumour treatment. Most perforations are recognised immediately and as a result 80% resolve with conservative treatment, but with considerable additional hospital stay and resource consumption; the remaining disruptions are rapidly and invariably fatal.[43,50] The risk is greatest in patients who have received prior radiotherapy or chemotherapy.[42] Other early complications are generally minor and rarely result in prolonged hospital stay or consumption of resources. The procedure-related mortality in studies is low (around 3%), but as most patients have multiple treatment sessions, the overall mortality for a patient receiving laser therapy may approach 10%.[49]

Late complications relate mainly to regrowth, which generally affects patients who survive for over 3-months; in these patients, further laser treatment or another palliative therapy is required to maintain swallowing. This need for repeated treatments with regular hospital attendance is the greatest drawback of laser therapy. Four outpatient treatment sessions spread over a 5-month period may not appear onerous, but these patients have terminal disease and any inconvenience is a burden. Repeated treatment of exophytic tumours may encourage submucosal growth, refractory to laser treatment, and often accounts for the fibrous stricturing encountered in late treatment failures. The overall stricture rate is quoted at 20%, rising to 50% when laser has been combined with radiotherapy; strictures are best managed by dilatation and stenting.[53]

Additional treatment
The additional use of radiotherapy or chemotherapy is appealing. The laser deals with the intraluminal disease, while radiotherapy or chemotherapy retards cancer regrowth and reduces the need for repeated laser sessions. External beam radiotherapy has been shown to be effective in this manner, but increases morbidity, and the benefits of reduced laser retreatment were outweighed by the need to attend the radiotherapy department repeatedly.[53,58,59] Similarly, additional intraluminal radiotherapy also increased the complication rate significantly in another study, with 30% of patients subsequently developing fibrous strictures.[59] A commonly held misconception is that the radiotherapy confers a survival benefit, but only one study has demonstrated improved survival in combined treatment patients; this was non-randomised and the effect was almost certainly due to selection bias.[46] Equally, the combination of laser and chemotherapy was shown to reduce laser retreatments in a different study, but gains were again offset by increased morbidity, and reattendance for treatment and follow-up, and there was no associated survival benefit.[49]

Seventy per cent of laser patients will require retreatment and 29% will receive a second modality of palliative treatment.[53] Laser 'failure' is probably best managed by mechanical techniques, as radiotherapy results are poor and responders still require dilatation for dysphagia relief. Cottier and colleagues reported a series of 28 patients who were intubated following laser failure, with improved swallowing in all and no complications secondary to intubation.[60] However, patients are still subject to tube-related late complications such as blockage and migration in comparable numbers to primary intubation.[4]

Secondary palliation
Laser therapy is itself an excellent additional therapy, with rapid and dramatic relief of dysphagia when other treatments have failed or tumour has recurred after curative surgery. Laser rapidly restores patency in stent-associated tumour overgrowth or ingrowth, with low associated morbidity. Cottier and colleagues used laser treatment for overgrowth following rigid intubation in nine patients, with no associated complications, and Sargeant and colleagues demonstrated that only one or two laser sessions successfully palliated intubated patients, with problems for a further 9 weeks.[60,61]

Summary
Laser therapy is rapid, safe and effective as a stand-alone, first line palliative treatment, with excellent relief of dysphagia, superior to that of rigid intubation, especially in the first 3 months of treatment. Morbidity and mortality rates are low, but laser ablation is technically demanding and time-consuming, and requires repeated treatment, which can be taxing for elderly, terminally ill patients. As such, laser is increasingly viewed as a complementary rather than a competing palliative therapy, to improve dysphagia before curative resection, to deal with postoperative recurrence or to manage overgrowth and ingrowth in patients with oesophageal stents.

Argon beam plasma coagulation
High-frequency diathermy electrocoagulation has become almost indispensable for surgical haemostasis. The application of this technology in therapeutic endoscopy has aided control of bleeding and allowed the development of procedures such as sphincterotomy, polypectomy and endomucosal resection. Similar techniques have been used with some success to debulk oesophageal tumours for palliation of malignant dysphagia. However, tissue adherence to the probe, the risk of damaging normal surrounding mucosa and the difficulty in controlling the depth of thermal injury are major problems with conventional diathermy.[62] Argon plasma coagulation (APC) uses the same principles, but transfers the electrical energy to tissue via a stream of charge-carrying ionised argon gas, and has been used for haemostasis in open surgery since the early 1990s. The development of probes that can be passed down an endoscope has meant that this technique can be directed visually at oesophageal tumours and as such bears greater similarity to laser treatment than to conventional diathermy.

An APC unit consists of a high-frequency alternating current generator, an argon gas source and a Teflon-coated applicator tube, which can be fed down the biopsy channel of a regular endoscope. The tip of the tube has a tungsten electrode, which ionises the stream of gas at an output voltage of 6500 V. The gas becomes electrically conductive, acting like a monopolar diathermy electrode and carrying charge in an arc to the tissue. Energy absorption leads to thermal damage and the current flows back to the unit via a large neutral electrode. The beam takes the path of least electrical resistance independent of the axial flow, thereby searching out areas where resistance is lowest. As a result, current can pass

tangentially from the electrode without any decrease in effectiveness. The depth of penetration is between 1 and 3 mm, and the formation of electrically resistant, desiccated eschar turns the beam towards fresh tissue, thereby reducing the risk of overtreatment of one area.[63]

Technique
The probe is protruded from the endoscope by 1 cm and placed 1–2 mm from the mucosal surface. The gas flow is 1–3 l/minute, so minimal insufflation and frequent suction is necessary to reduce gastric distension.[64] Retrograde treatment is applied, with 20–30% requiring predilatation to allow the endoscope to pass.[65] The tumour is coagulated and the endoscope passed through to abrade the eschar so that further treatment can be given in one session. The patient is allowed fluids on the same evening and food on the following day, and treatment is repeated every 3–4 weeks as necessary.

Effectiveness
APC has a short learning curve and operator confidence is high given the low perforation risk, homogeneous depth of penetration and excellent view provided by the bioillumination of the ionised argon beam. Electrocautery is a familiar concept to most operators and the working distance from the tumour with minimal tissue adherence ensures good control. APC is applied in a brushwork rather than pinpoint fashion, so accuracy is less important than laser, and since the beam moves itself to fresh areas it can be applied round corners so that difficult stenotic tumours can be easily treated. Because of these factors APC has a technical success rate of over 80%.[66] The lower generated temperatures mean that it is less suitable than laser for rapid debulking, but recanalisation is achievable for the majority in one session and only two to six sessions will be required per patient over the course of their palliative care.[62,65-67] Heindorff and colleagues demonstrated that 58% of patients are palliated to a normal diet by one session, 25% require further sessions and functional failure occurs in 13%.[66] The quality of dysphagia relief is excellent and comparable to laser treatment, although 60–70% of patients develop recurrent dysphagia requiring repeated APC treatments and up to 29% will require an additional second type of treatment.[47,48,53,68] Robertson and colleagues showed that APC sessions alone maintained palliation until death in 64%, but that 36% required an additional palliative treatment.[65] APC, similarly to laser, is most effective for straight, short (<5 cm), midoesophageal, exophytic tumours.

Complications
The complication rate is low, with procedure-related perforation again comparable to laser, with a rate of 6–10%, most of which can be successfully managed conservatively.[65,66,69,70] Predilatation accounts for the majority of perforations as the depth of the APC thermal penetration is quite superficial and well controlled.[63,66,69]

Additional treatment
APC is outstanding in the treatment of overgrowth and ingrowth, with rapid restoration of luminal patency and minimal morbidity.[71–73] In this regard, it is preferable to laser therapy as lower temperatures generated are less likely to cause damage to the underlying stent.[60]

Summary
APC is as safe and effective as laser therapy as a first line palliative treatment, with near-normal relief of dysphagia. Owing to the lower cost, availability, ease of use, low morbidity profile and short learning curve it is replacing laser as the primary debulking treatment. Unfortunately, as with laser treatment it is time consuming and there is a need for repeated treatments.

Bipolar electrocoagulation
Another solution to circumvent the problem of tissue adherence to diathermy electrocoagulation probes was the development of the bipolar electrocoagulation (BICAP®) probe by Johnston and colleagues. The probe is similar to an Eder–Puestow dilator with a plastic olive attached to a hollow flexible shaft. The central portion of the olive is encircled by a 1-cm metal electrode strip, which can be connected to an external electrocoagulation unit. The passage of electrical current leads to heat generation and thus thermal tumour destruction. The depth of tissue damage (usually in the order of 2–4 mm) is dependent on the power setting, the appositional force and the duration of the treatment pulse. BICAP probes come in a variety of diameters (6–15 mm), with a 180° or 360° applicator surface.[74]

Technique
The technique is straightforward and easy to learn. Endoscopy is carried out under sedation and fluoroscopy, to define tumour geography and place a guidewire, with dilatation where necessary. Retrograde, sequential diathermy burns are carried out at 1-cm intervals using the largest diameter passable probe to ensure close application to the tumour surface. Each treatment takes a few seconds at each station, so that a 5-cm tumour will require five stations of 5–20 seconds

each, guided by centimetre marks on the shaft of the probe. The olive remains hot, so it is left to cool for a short period before withdrawal. Once the treatment is completed, endoscopy is used to check treatment and immediate retreatment may be given if appropriate. The procedure takes approximately 30 minutes and is well tolerated under sedation.

Effectiveness

Few effectiveness studies have been published on small numbers of patients. Johnston and colleagues, who developed the probe, demonstrated improved swallowing in 20 patients with obstructing, circumferential cancers in a mean of 1.7 treatment sessions, the effect lasting for 7.6 weeks before repeat treatment was necessary, but unfortunately, two patients suffered severe, delayed haemorrhage and two developed oesophago–pulmonary fistulae.[75] Jensen and colleagues demonstrated technical success in 90% of 14 carefully selected patients, with 86% managing a soft or solid diet following treatment and the effect lasting for 4–10 weeks.[76] However, one-third of the patients referred for treatment were not suitable for BICAP and were excluded from the study, and one patient developed an aerodigestive fistula following treatment at the margin of the tumour in an area of adjacent normal mucosa.[76] McIntyre and colleagues treated 17 selected patients with BICAP: 82% were able to swallow soft foods or better after one treatment and after retreatment this rose to 94%, but retreatment was required every 28 days, and although there were no BICAP-related perforations, one patient suffered a perforation due to pretreatment dilatation and one patient developed a tracheo-oesophageal fistula.[74] In another study, swallowing improved in 86.7% of patients, but there was one fatal haemorrhage and two tracheo-oesophageal fistulae, with retreatment necessary every 18 days.[77] Perforation, fistula formation and haemorrhage appear major drawbacks, with rates of 20%, and probe–tissue adherence remains a problem.[75,76,78] The development of late strictures has only been noted in one human study, where a proximal treatment margin stricture was noted in 12.5% (n = 2/16).[52]

Summary

Published BICAP series are small and purely observational, but it appears to be a technically straightforward procedure with the advantage of treating large areas rapidly, and the equipment is portable, robust, easy to maintain and inexpensive. It is suited to treating long, circumferential strictures with submucosal spread and for cervical disease, an area poorly palliated by other modalities, but the need for radiographic screening and unpredictable results mean that it is not a dramatic improvement over dilatation alone. Although BICAP is effective and well tolerated in selected patients, major complications are common, especially in non-circumferential tumours where treatment may be inadvertently given to normal mucosa at the tumour margins.

Photodynamic therapy

The role of palliative photodynamic therapy (PDT) is yet to be fully determined as it is still experimental and under evaluation. PDT is a modification of conventional laser based on the selective retention of a photosensitising chemical in tumour tissue. This chemical is activated by a specific wavelength light in the presence of molecular oxygen to produce cytotoxic, oxygen free radicals that cause microvessel damage leading to tissue ischaemia and necrosis. This is a photochemical effect, with tumour tissue damaged preferentially since the photosensitising chemical is retained twice as long in dysplastic and neoplastic tissue.

Technique

A haematoporphyrin derivative (dihaematoporphyrin ether or porfimer sodium, Photofrin®) is the most commonly used photosensitising agent, which is given intravenously as an outpatient procedure 1–3 days before the light application. The light source is a cylindrical diffuser incorporated into the end of a quartz fibre, which is placed through the biopsy channel of a standard endoscope. This circumferentially transmits monochromatic (630 nm) light to the oesophagus. The diffuser is 2.5 cm long, so sequential treatments are necessary for long tumours. Dosimetry studies have developed the depth of necrosis for a given light dose so as to determine the efficacy and toxicity profile.[79] Endoscopy is repeated after 48–72 hours to débride any necrotic tissue and give a second light application if necessary. Adjacent normal mucosa may become oedematous or develop ulceration, but rapidly regenerates. Maximum symptomatic relief is achieved by 1 week and recurrence of obstruction can be retreated by PDT as long as 1 month has elapsed since the last photosensitising injection.

Effectiveness

Early PDT studies were promising, with technical success consistently over 90%.[79–81] However, results were inconsistent. Heier and colleagues demonstrated that 95% of PDT-treated patients

had either no dysphagia or dysphagia to solids only at 1 week following treatment, but Lightdale and colleagues, in a large, rigorous study, demonstrated dysphagia relief in only 44% of patients and 25% experienced no change in swallowing ability.[79,81] However, this study was conducted in 24 separate centres. In comparison, Luketich and colleagues reviewed 77 patients treated with PDT over only a 2-year period in a single centre, with 91% effectiveness and a mean dysphagia-free interval of 80 days.[80]

Complications

All studies report high complication rates, with up to 29% of patients having major adverse events.[82] McCaughan and colleagues palliated 58 patients with PDT, but four patients developed an aerodigestive fistula (7%), one died from severe oesophageal haemorrhage (2%), fibrous strictures developed in a further four patients and minor burns were seen from photosensitivity reactions.[83] Maier and colleagues retrospectively reviewed palliative PDT in 44 patients and noted major treatment related complications in 9.2%, with four perforations and four patients developing oesophagorespiratory fistulae.[84] In contrast, in a study by Moghissi and colleagues, no PDT-related mortality was reported in 65 patients, but 89% (n = 58) received other treatments before PDT.[85] This unpredictability of treatment is due to variations in tissue light attenuation, tumour uptake of photosensitiser and oxygen availability, which can easily lead to overtreatment with considerable associated morbidity and mortality. Mediastinitis and aerodigestive fistulae are the most hazardous complications, but exposure of normal tissue at the margins of the tumour can lead to painful ulceration and strictures. Solar photosensitivity, although rarely life-threatening, also has significant social implications and can persist for 8 weeks following treatment, so that patients remain indoors to avoid painful sunlight exposure skin reactions.

Summary

PDT has significant theoretical advantages in palliation. It uses a selective technique that targets tumour tissue and limits damage to adjacent normal tissue. It is pain free and less operator dependent or technically demanding than conventional ablative techniques. It is useful in cervical disease or for long or angulated tumours where endoscopic treatments are poorly tolerated and technically difficult. It treats submucosal disease well as the diffuser light permeates into tissue that conventional laser would not reach. However, PDT is expensive and associated with unacceptable toxicity. The induced, iatrogenic porphyria is a major drawback, limiting light exposure for up to 8 weeks, and with treatment required every 4–6 weeks to maintain palliation, this almost entails staying indoors to avoid photosensitivity reactions for life. As a result, it is likely that PDT will not be suitable for palliation and will remain in experimental use for Barrett's oesophagus and the treatment of early oesophageal tumours.

Ethanol-induced tumour necrosis

Ethanol-induced tumour necrosis (ETN) is a simple, readily available palliative treatment. Endoscopy is performed under intravenous sedation, after dilatation where necessary, and 0.5–1-ml aliquots of 100% ethanol are injected into all visible tumour tissue (average 8–10 ml ethanol per session) using a standard injector assembly. Tumour necrosis occurs rapidly, with relief of dysphagia within a week. The procedure can be repeated as necessary after an interval of 3–7 days.

Few studies have been published, but functional success is reported at over 80%.[86–88] Nwokolo and colleagues treated 32 patients with ETN, and 90% could swallow a soft diet and 72% a near-normal diet, and 31% were dysphagia free after a median of one treatment session (range 1–3).[87] Dysphagia relief was maintained by repeating treatment every 28.5 days (median, range 4–170) and no procedure-related complications were seen despite pretreatment dilatation in 41%.[87] Similarly, Chung and colleagues treated 36 patients with ETN, with an improved mean dysphagia score and a mean duration of palliation of 35 days.[86]

ETN requires no additional investment for most endoscopy units, requires minimal hospitalisation, is easy to perform and major complications are uncommon. Best results are seen with polypoid, exophytic lesions, and it is also suitable for cervical tumours as long as a reasonable view of the tumour is possible. However, the pattern of tumour necrosis is unpredictable and repetitive treatments are necessary. With only a month before symptom recurrence, ETN is not vastly different to simple dilatation.

An evolution of ETN is the direct intratumoral injection of cytotoxic chemotherapeutic agents. This has arisen from potentially curative treatments for early cancers in Japan. In a pilot study of five patients, Wright and colleagues injected a solution of 5-fluorouracil (5-FU) and 2.5% sodium morrhuate into advanced SCC.[89]

Tissue necrosis occurred in three patients, but the effect lasted for less than 1 month despite repeated injections at 3–7-day intervals.[89] In a similar study, Monga and colleagues administered cisplatin/epinephrine gel endoscopic injections in nine patients with advanced oesophageal cancer. Dysphagia resolved to difficulty with solids in eight patients 89%. This appears as safe and effective as ethanol, but is considerably more expensive. This may hold promise for the future with the development of different agents.[90]

Radiotherapy

Radiotherapy is an effective palliative treatment used to recanalise the oesophagus through tumour destruction and inhibition of further growth. Impressive responses are possible, but the effects vary tremendously with dose, technique and the individual patient response. The difficulty in evaluating results is that there are no constants between studies: various techniques are used at various doses for various stages of various histology cancers, and most studies have been based on potential cure. Studies of palliation invariably use radiotherapy as an additional treatment to other modalities.[91,92] Radiotherapy to the oesophagus can be given either externally or intraluminally, and these are considered separately. SCC appeared on initial studies to be more radiosensitive than adenocarcinoma; however, recent studies do not confirm this.[68,93–95]

External beam radiotherapy

External beam radiotherapy (EBRT) is popular and widely used as it utilises existing facilities and is straightforward to plan and execute, with minimal disruption for the patient and no overnight stay. Studies as primary palliation are scarce and results are erratic as up to 50% of oesophageal cancers do not respond and doses are limited by the close proximity of the lungs and spinal cord.[96–101] Despite this, Stoller and Brumwell showed that the palliation from radiotherapy was equivalent to that of palliative surgery, but with lower associated morbidity and mortality.[97]

Regimens are based on 30–60 Gy in ten or more fractions given over a 5–6-week period, with multiple hospital visits. Less than 30 Gy produces negligible effects and more than 60 Gy leads to unacceptable morbidity.[39] Swallowing deteriorates immediately after treatment owing to inflammatory oedema, but improves thereafter to give a maximum benefit at 4–6 weeks. In 245 advanced cases Kelsen found that dysphagia could be improved in 50% for between 2 and 6 months, although failure was most likely in locally advanced cases, which unfortunately represents the most common situation.[102] Caspers and colleagues treated 127 patients with EBRT alone: 70.5% of the patients showed improvement of dysphagia, 54% until death, and there appeared to be a survival benefit in those treated with higher doses.[100] However, in a smaller series, only 41% of 81 patients were palliated successfully with EBRT alone, the duration of dysphagia relief being dose dependent.[99] Langer and colleagues similarly demonstrated that the local failure rate was higher with lower doses.[98] As such, the effectiveness of EBRT improves at higher radiation dose, with the possibility of a survival benefit but at a cost of increased morbidity. Unfortunately, morbidity is common regardless of dose, with all patients experiencing some malaise and oesophagitis and 30% developing severe ulcerative oesophagitis.[103] Treatment leads to intractable nausea and vomiting if the fields include the stomach, and fibrous cicatrisation requiring dilatation or salvage intubation occurs in 30–50%, especially with higher doses.[104,105] As a result of this morbidity, 30% of patients starting a course of oesophageal radiotherapy do not complete it.[68] Treatment-related mortality is rare, but mortality figures may be distorted as treatment is usually terminated when a patient becomes too ill to continue.[106]

The advantages of EBRT are the potential for a dramatic response with a low mortality, the ability to perform treatment as an outpatient and the ease of combination with other palliation modalities. However, dysphagia relief is unpredictable, with a long overall treatment time and a long time to initiate these effects, and many patients are seen to relapse rapidly after treatment.[91] Morbidity rates are also considerable, leading to a high 'failure to complete treatment' rate. Intensive multiple fractions per day treatment may become preferable in the future for a swifter, more predictable palliative effect and shorter treatment times.[107]

Brachytherapy

Placing the radiotherapy source closer to the tumour maximises the tumour radiation dose while minimising damage to local dose-limiting structures. This is termed brachytherapy and is possible in oesophageal cancer by placement of an intraluminal radiotherapy source. This also ensures that the relatively hypoxic, luminal component of the disease, which is naturally more radioresistant, is subjected to the highest dose. The radioactive source is pneumatically or mechanically transferred to an applicator placed by the tumour. Staff are not exposed to the

radiation, making the procedure safe, fast and simple. Treatment is usually given as a single dose-fraction of 10–15 Gy at 1 cm off-axis with a treatment length of 10 cm, although multiple fractions and higher doses have been experimented with.[108] The tumour is precisely mapped by endoscopy, fluoroscopy and CT, and treatment planned to incorporate a few centimetres of normal oesophagus at either end. The applicator is a small, graduated nasogastric-type tube (8 mm diameter) positioned with fluoroscopic control over an endoscopically placed guidewire under sedation, with predilatation if necessary to allow easy passage of the endoscope and guidewire. Radiographs may be taken with a dummy source *in situ* to verify position. The applicator is immobilised using a specially cast face mould, then connected to an afterloading machine to control the transfer of the source through the applicator. Computerised planning calculates the dose delivery and dwell time of the source within the applicator. The source is high-dose rate iridium[192] wire, so that treatment takes only a few minutes, with staff safely observing the procedure by closed circuit television. Once treatment is complete, the applicator is disconnected and withdrawn, with routine recovery of the patient.

Only a handful of studies have been published on brachytherapy as sole treatment, as most studies combine EBRT with a local brachytherapy tumour boost.[109–117] Rowland and Pagliero treated 40 patients, with 65% successfully palliated for 12–15 weeks with no associated mortality, although 12.5% developed significant oesophagitis.[109] Fleischman and colleagues successfully palliated nine out of ten patients, most of whom had failed previous other palliative treatments, but 50% suffered with troublesome oesophagitis.[110,113] Jager and colleagues used brachytherapy in 36 patients, improving swallowing in 61%, but six patients required further irradiation and another six required salvage palliation with rigid intubation.[118] This study was continued for a further 5 years (treating a total of 75 patients), and although 67% had effective dysphagia relief additional palliation was necessary in 56% and serious morbidity occurred in 9%.[111]

Oesophageal brachytherapy remains in limited use, but is straightforward, quick and relatively inexpensive, and treatment can be given on an outpatient basis. It appears to be safe, using remote-controlled, automated afterloading machines with a low mortality. It can also be combined with other palliation modalities; however, dysphagia relief remains unpredictable and morbidity is high. Further studies are required.

Combination radiotherapy

By combining EBRT and brachytherapy the benefits of both can be garnered, increasing tumour cell-kill while sparing normal tissue. Brachytherapy is usually given after EBRT. Agrawal and colleagues treated 67 patients with EBRT (20–50 Gy in five to 20 fractions over 1–4 weeks) followed by brachytherapy (10 Gy at 1 cm). This restored swallowing in 92%, but 55.7% required subsequent dilatation and 6% developed aerodigestive fistulae after treatment.[95] Similarly, Caspers and colleagues treated 35 patients with combination radiotherapy: 91% were able to eat solids, but 14% required hospitalisation for oesophagitis.[116] In a historical comparison, Petrovich and colleagues demonstrated that 76% of 46 patients treated with combined radiotherapy had effective palliation versus 52% treated with EBRT alone.[101] In contrast, Pakisch and colleagues used brachytherapy followed by EBRT in 48 patients, achieving satisfactory palliation in 96% with dose-related complication rates.[119] Taal and colleagues also gave brachytherapy first and demonstrated a rapid and excellent response, with 60% gaining complete remission from dysphagia; however, 60% encountered severe side-effects and there was significant mortality. The same group performed a subsequent study using smaller dose fractions but the same total dose, and this reduced the complication rate to 17% while maintaining the overall response (83%). This illustrates the small therapeutic margins and the impact of the fraction per dose.[115]

These studies demonstrate that in a fit patient, a combination of EBRT with an intraluminal boost of brachytherapy may be superior to either treatment alone, but dose rates, techniques and fractionation are of paramount importance for morbidity.

Summary

Radiotherapy is an effective form of palliation and impressive results are possible, but the effects vary tremendously with dose, technique and the individual response of patients. The promise of potential cure means that radiotherapy has not been subjected to adequate investigative research in a palliative population. Despite this, EBRT is widely used for palliation as it uses existing facilities. It is associated with low mortality, can be performed as an outpatient procedure and can be combined with other palliative modalities.

However, it involves long treatment times, has a delay to take effect and is associated with an unpredictable response which may be short lived, and considerable morbidity and rapid recurrence of symptoms are not uncommon; as such, failure to complete treatment is common. Intraluminal radiotherapy, brachytherapy, has been subjected to even less research and remains in limited use owing to a scarcity of expensive equipment, but it appears to be straightforward, quick, relatively inexpensive to run and safe. As with EBRT, it is associated with low mortality, outpatient treatment and ease of combination with other palliation, but dysphagia relief is again unpredictable and morbidity is high. Combining treatments may improve response rates, but further studies are necessary to determine optimum dose rates, techniques and fractionation to obtain the maximum effect for minimum morbidity.

Chemotherapy and chemoradiotherapy

Chemotherapeutic agents destroy tumour tissue and can therefore relieve intraluminal dysphagia, but since most patients with advanced disease present in a poor clinical condition they are unsuitable for the rigours of most chemotherapy regimens. Few studies have been performed and almost all focus on potential cure in young, fit patients, by a combination of chemotherapy and radical radiotherapy. These studies are hard to interpret in regard to pure palliative effects, since many combine with other palliative therapies and use a variety of different therapeutic protocols. Selection bias is also a problem, as fitter patients than the average oesophageal cancer population are studied and any favourable results reflect this. Tumour control and survival benefits have been reported, but compliance is poor owing to toxicity and lengthy treatment times, and morbidity and quality of life effects are not discussed. As a result, it is difficult to draw pertinent conclusions as to the efficacy of chemotherapy in cure, let alone palliation.[102,120–122]

The most favourable response rates are with cisplatin-based combinations: responses with single-agent therapy such as bleomycin, methotrexate, 5-FU, and vindesine do not exceed 30%, but rise to 30–60% when cisplatin is added.[33,39,123,124] However, response is not a good indicator of clinical effect, which may be short lived, and toxicity is always a problem. This is demonstrated by Bleiberg and colleagues, who randomised patients with locally advanced or metastatic squamous oesophageal cancer to cisplatin alone or in combination with 5-FU; the response rate was 35% for combination chemotherapy versus 19% for cisplatin alone, but this did not translate into a survival advantage and toxicity was frequent and severe with combination treatment, with seven treatment-related deaths (16%).[125] In palliative terms, Spiridonidis and colleagues used a combination cisplatin treatment in 18 patients, achieving reasonable dysphagia relief in 89%, but with high toxicity and one treatment-related death (5.5%).[126] The response to epirubicin, cisplatin and 5-FU chemotherapy in a study by Highley and colleagues was 59%, with improved swallowing as a result.[127] Modern agents such as paclitaxel, irinotecan and lobaplatin may improve response rates further.[128]

Chemoradiotherapy

The combination of radiotherapy and chemotherapy is appealing, with effects on both local and systemic disease added to chemotherapeutic radiosensitisation of tumour.[91] Coia and colleagues treated 20 patients with palliative chemoradiotherapy using 5-FU and mitomycin C; 82% had no dysphagia post-treatment and 64% remained dysphagia free until death or last follow-up, but toxicity including oesophagitis, stomatitis, oral candidiasis, thrombocytopenia and neutropenia was common and disabling, and there was one associated perforation, two patients developed tracheo-oesophageal fistulae and two patients developed radiation pneumonitis.[93,129] By 1991, Coia and colleagues had treated a total of 33 patients with palliative chemoradiotherapy; 77% were rendered dysphagia free, 60% until death, with a median dysphagia-free duration of 5 months, and although 56% had moderate to severe toxicity this was mostly transient and only 12.2% developed severe toxicity with 3.3% requiring hospitalisation as a result.[94] Treatment mortality was less than 2%, but this is difficult to interpret as treatment was stopped when patients became ill.[130] In a well-known and often quoted study, Herskovic and colleagues also reported a high rate of severe (44%) or life-threatening (20%) side-effects, with only 58% having improved dysphagia using a curative chemotherapy regimen.[91] Calais and colleagues gave chemoradiotherapy to 53 patients (60 Gy of EBRT and three cycles of cisplatin, 5-FU and mitomycin C, followed by 10 Gy of high-dose rate brachytherapy), with improvement in swallowing in 75%, but severe toxicity in 30% and mortality in 2%.[131]

The lack of thorough randomised studies and data means that chemotherapy and chemoradiotherapy for the palliation of oesophageal cancer cannot yet

be supported. Brief and modest improvements in dysphagia and possible survival benefits are offset by considerable side-effects and substantial treatment times for patients with a short lifespan and a labile quality of life. More effective agents and treatment strategies need to be evaluated formally with sensitive response and quality of life analysis before acceptance.

Mechanical techniques

Dilatation

By far the most common palliative treatment is dilatation of the oesophagus, but this is a temporary procedure that is rarely used alone or definitively. Dilatation is frequently used before a full endoscopic oesophagogastric assessment as a part of preoperative staging, especially since the introduction of oesophageal endoscopic ultrasound, and also before many forms of definitive palliative treatment such as rigid intubation.

Dilatation is safe, cheap and easy, and is usually performed as an outpatient procedure under intravenous sedation. A guidewire is passed through the oesophageal lumen under endoscopic vision, ideally with fluoroscopic visualisation. Various dilators are available on the market, but Savary–Gilliard type dilators are felt to be the safest variety. These soft plastic dilators are progressively wider along their length and are passed over the guidewire to a maximum of 15 mm.[132] Immediate relief of dysphagia is effected with one treatment, although the duration of relief is short and nearly all patients will require further treatment after 4 weeks, regardless of the diameter of the initial dilatation.[133] Dilatation is easily repeatable, but the benefits diminish with subsequent procedures and up to 22% require a further treatment such as intubation owing to insufficient palliation by dilatation or owing to complications.[133] Soft, fleshy tumours respond poorly and dilatation should be avoided in these cases.[134] Studies of dilatation are scarce and observational, with considerable variation in results. Of 128 dilatations in 41 oesophageal cancer patients by Lundell and colleagues, six perforations occurred (5%), but Heit and colleagues performed 616 dilatations in 26 patients with only one perforation (<0.01%); this probably reflects the benefit of fluoroscopic guidance.[133,135]

In summary, dilatation is simple, safe, cheap, suitable for nearly all tumours and effective in one session, with a low complication and mortality rate, but offers only temporary relief.

Rigid intubation

Internally lodged tubes have been used to maintain nutrition in oesophageal cancer patients since the beginning of the twentieth century. Initially, these tubes were placed by pulsion through the tumour using a rigid endoscope.[136] The development of oesophageal surgery led to pull-through tubes placed at the time of laparotomy; however, mortality was as high as 45% with this approach and the immunosuppressive and catabolic effects of the associated laparotomy adversely affected survival.[137–144] Peroral pulsion techniques were revisited with the development of the fibre-optic endoscope and intubation has since become the most widely used palliative treatment worldwide.[139,145] The immediate relief from dysphagia is especially useful in the elderly, where minimal hospital attendance is a priority.[40,146–148] Various materials and designs have been used over the years, from ivory to German silver, but all are currently made from reinforced plastic with flanges at the ends to reduce migration.

Technique

All patients are sedated and a guidewire is endoscopically placed across the tumour. Since a luminal diameter of at least 15 mm is required for placement, most tumours require predilatation. The proximal and distal margins of the malignant stricture are measured endoscopically and either marked externally using radiopaque skin markers or internally by injecting contrast material submucosally (e.g. Lipiodol). An appropriate length tube is selected and inserted over the guidewire under fluoroscopic guidance. Placement can be checked endoscopically and radiologically and the prosthesis moved or removed using a repositioning balloon. Patients are recovered and discharged when eating and drinking, sometimes on the same day, but usually after an overnight stay.

Effectiveness

Since rigid tubes have been used for the palliation of oesophageal cancer for over 75 years there have been many observational studies published, but comparatively few randomised trials. Rigid intubation is straightforward, easy to learn and quick to perform with immediate results. Technical success approaches 100%, with functional success in over 90% that is usually maintained until death.[4,40,75,143,149–153] Rigid intubation can be used for external compression owing to the radial strength of the tubes, to seal aerodigestive fistulae by using a cuffed tube and for long or tortuous strictures, although best results are obtained for middle third tumours. It is especially useful as a

salvage procedure when other palliative modalities have failed.[61,151,154] Poorest results occur when tubes are placed at the extremes of the oesophagus, as this can lead to a foreign body sensation when placed near cricopharyngeus and migration and reflux oesophagitis if placed at the oesophagogastric junction.

However, rigid intubation has many drawbacks. The quality of the swallowed diet is limited by the small internal diameter (10–12 mm) of the tubes and only 20–30% of patients return to a completely normal diet after treatment, with 20% only able to swallow liquids.[68,142,146,153] Morbidity is high and up to 29% of patients will require additional procedures after initial tube placement owing to complications.[40] Perforation is the most serious complication, occurring in up to 13% of tube placement procedures.[4,40,72,132,141,143,146,147,151,155–157] If perforation is noted at the time of the procedure, then correct placement of the prosthesis may help to seal the tear, as most are small, and conservative management is successful in 66–94%.[72,143,151,154,156,158] Late perforation is also possible in 1–8% owing to pressure necrosis and can be fatal if aortic erosion occurs.[72,151] Since only radial force and the flange friction secure the tube, migration occurs in up to 30%, higher when used for soft, polypoid or necrotic tumours.[40,72,141,143,146,147,149,151,159,160] Tube blockage is also common either by tumour overgrowth or by food bolus obstruction. Overgrowth requiring clearance or tube replacement occurs in 6–17% and food bolus obstruction in 7–19%.[28,40,72,143,151] Acid reflux is possible if the tube crosses the gastro-oesophageal junction, leading to painful oesophagitis in 2%, but the potential to aspirate gastric contents may account for many early, unexplained deaths.[40,146,151]

Procedure-related mortality lies between 2 and 27%, mostly secondary to perforation or aspiration.[28,40,72,147,151,156,157,161] The nutritional state of the patient, the tumour length, and angulation and respiratory tract involvement were significantly associated with mortality in a study of 181 patients.[157] As such, careful selection and awareness of potential problems can reduce associated mortality.[162] This is well illustrated by a literature review of 2459 patients palliated with rigid tubes in 1974, which quoted an overall in-hospital mortality of 13.9%, but by 1994 this had fallen to 8% and a contemporary study using modern prostheses had a procedural mortality of only 2.8%.[40,150,156]

Additional treatment
Although the additional use of radiotherapy appeared to offer a survival advantage in one study, this was subject to selection bias and randomised studies have failed to achieve any benefit with additional radiotherapy or chemotherapy; one prospective, randomised trial had to be terminated prematurely because of a negative survival effect in intubated patients receiving chemotherapy.[163–166] Furthermore, the survival advantage is unlikely to compensate for the increased morbidity, protracted hospital stay and need for repeated hospital attendance.[151,163,167,168]

Summary
Rigid intubation changed palliation irrevocably, with rapid, lasting palliation of dysphagia in one endoscopic session. However, the pulsion technique with predilatation, is traumatic and associated with a risk of perforation and considerable morbidity.[151] Lasting dysphagia relief may be effected, but the quality of swallowing is limited by the small available lumen, and late complications that necessitate readmission and reinterventions, such as tube blockage and migration, are common. However, previously published poor morbidity and mortality figures reflect the unselected nature of patients who are treated by intubation, which is frequently reserved for elderly patients with total dysphagia and as salvage therapy after failure of other treatment modalities, all situations where any treatment would perform badly. Newer insertion techniques have lowered mortality, and morbidity and mean that intubation can be performed as an outpatient procedure.[169] It is quick and easy, with immediate relief of dysphagia in a single session and no need to reattend unless complications develop.[141,154] It remains the accepted standard treatment in many centres.

Self-expanding metal stents

Ever since the first rigid tube was placed for the palliation of oesophageal cancer, tube design has varied to offset drawbacks inherent to tube construction and placement. Modern tube designs use thick, reinforced, plastic walls to maintain radial rigidity, thereby reducing the available lumen and offsetting the primary objective of the prosthesis. Tubes remain at maximal diameter during placement and as a result carry a high perforation risk, a need for predilatation, and are subject to migration. To counteract these disadvantages, researchers experimented with expanding metal mesh stents. The concept is of a tube (diameter 18–24 mm)

that can be compressed and restrained in a delivery device of much smaller diameter (6–12 mm) that can be safely introduced across a tumour without predilatation. The removal of the restraining device allows controlled, radial expansion to a large diameter with rapid palliation of symptoms similar to that of a rigid tube. The width of the stent is not limited by the width of the introducing equipment, and an inherently strong expansile force and rough outer surface reduce migration. The stent wall is thin, so a greater internal diameter is possible for a smaller external diameter giving a wider available lumen for improved quality of swallowing. Early results were excellent and self-expanding metal stents (SEMS) have supplanted conventional rigid tubes in many institutions as the palliative treatment of choice.[170–172] However, these results are now being questioned, as there is evidence to suggest that SEMS do not improve dysphagia to the extent expected and are associated with late complications and troublesome postinsertion pain.[173,174] They are also considerably more expensive (approximately £1000) than rigid tubes (approximately £100). As such, unless they are more effective at relieving dysphagia and have a lower reintervention rate, then the expanse may not be worth the expense.

There are three main SEMS designs:

1. sprung metal mesh, usually stainless steel (e.g. Wallstent)
2. memory metal mesh, usually nitinol, an alloy of titanium and nickel (e.g. Ultraflex)
3. a metal spring (e.g. Esophacoil).

There has been no prospective randomised study comparing one stent with another.

Wallstent® Esophageal II Endoprosthesis (Microvasive, Boston Medical) is a braided stainless steel mesh covered with polyurethane except for 1 cm at each end. The shaft diameter is 18 or 22 mm, flaring to 28 mm. It is popular with UK radiologists, as the steel construction is radiopaque and the design easily recaptured if less than 50% has been deployed, to allow repositioning. It comes in lengths of 10 and 15 cm after 20–25% longitudinal shortening on deployment. The Flamingo stent is a derivative of the Wallstent, with a conical shape developed to overcome distal migration; however, proximal migration is common and the medical devices agency advises against placement except in the distal oesophagus.

Gianturco Z-stent® also uses stainless steel configured into 2-cm zigzag-shaped segments attached consecutively to each other and entirely covered in a polyurethane/polyethylene coat. One or two rings of lateral barbs on the outside of the stent reduce migration. The stent comes in lengths of 6, 8, 10, 12 and 14 cm and two shaft diameters, 18 mm flared to 21 mm or 25 mm flared to 27 mm. The Gianturco Z-Stent does not shorten on deployment, so is especially useful for accurate placement.

Ultraflex® Esophageal Stent System (Microvasive, Boston Medical) is a single-strand, knitted memory metal (nitinol) mesh stent which exerts a more gentle radial expansion pressure than other SEMS and can be used with an optional external polyurethane coat. It can be deployed by distal or proximal release mechanisms under endoscopic visualisation and the low expansile force means that repositioning is possible after release.

Esophacoil® is a nitinol spiral with a very strong expansile force useful for extrinsic compression, but has been associated with significant postinsertional pain in up to 73%.[148,175–177] Marked shortening of up to 50% occurs on deployment and the delivery system has been criticised for being bulky and stiff, with a high rate of dysfunction, up to 46%. Mucosal strangulation was noted with early deployment systems and tumour ingrowth was also common.[178] As a result, the Esophacoil was withdrawn from the UK market in 2001.

Technique

Insertion of SEMS is similar to that of a rigid tube. The entire length of the stenosis is precisely determined by endoscopy and fluoroscopy after sedation. Wallstents and Z-stents need no more than a 10-mm lumen to be deployed as they produce sufficient radial expansile force to expand gradually to full diameter even in tight strictures and excessive dilatation may result in increased migration, whereas lower expansile Ultraflex stents require dilatation to 15 mm preinsertion.[179] The proximal and distal margins of the malignant stricture are measured and marked and a stiff guidewire is placed across the tumour. An appropriately sized SEMS is selected and inserted over the guidewire so that the proximal funnel of the stent sits above the proximal extent of the tumour. Placement is checked endoscopically and radiologically. Some clinicians use a dilating balloon to expand the stent fully to ease postinsertion pain (Shepherd H, Royal Hampshire County Hospital: personal communication). Patients are discharged when eating and drinking without pain.

TABLE 2 *Effectiveness of SEMS for palliation*

Reference	Patients	Technical success	Functional success	Mortality	Morbidity
Knyrim *et al.*, 1993[180]	21	100%	92–100%	0	0
Ellul *et al.*, 1995[181]	33	100%	100%	3%	12%
Saxon *et al.*, 1995[182]	52	96%	96%	7.7%	9.6%
De Palma *et al.*, 1996[183]	19	94.7%	100%	0	0
Kozarek *et al.*, 1996[184]	38	ND	ND	3%	5%
Moores and Ilves, 1996[185]	20	100%	100%	5%	5%
May *et al.*, 1996[186]	30	100%	83%	3.3%	30%
Mason, 1996[43]	106	100%	100%	5%	3–12%
Feins *et al.*, 1996[187]	13	100%	92.3%	7.7%	15.4%
Kinsman *et al.*, 1996[188]	59	100%	90%	8.5%	15%
Raijman *et al.*, 1997[179]	60	98.3%	100%	0	8.3%
Schmassmann *et al.*, 1997[189]	82	97.6%	ND	8.5%	20.7%
Wengrower *et al.*, 1998[190]	81	100%	96%	0	3.7%
Davies *et al.*, 1998[191]	41	100%	100%	0	15%
Cowling *et al.*, 1998[192]	70	100%	95%	4.3%	ND
Lam *et al.*, 1999[193]	82	98%	100%	2.4%	8.5%
Olsen *et al.*, 1999[194]	30	97%	100%	3.3%	10%
Siersema *et al.*, 2000[174]	40	100%	100%	ND	18%
Toikkanen *et al.*, 2000[195]	58	100%	98%	0	ND
Singhvi *et al.*, 2000[196]	50	100%	98%	4%	8%
Bartelsman *et al.*, 2000[197]	153	100%	100%	3.3%	7–30%
Christie *et al.*, 2001[198]	100	100%	85%	1%	5.5%
Overall	1238	99%	96%	3.3%	10.5%

Effectiveness

Table 2 summarises the results from the larger or more thorough SEMS studies. Mortality is procedure-related mortality and morbidity, where possible, is all major early morbidity that would have resulted in a prolonged admission.

SEMS are straightforward to deploy and technical success approaches 100%, with no major differences between designs. However, success may be achieved at a cost since published figures frequently neglect to mention the need for immediate stent replacement or the use of more than one stent. For example, Kinsman and colleagues quoted 100% technical success despite one immediate migration requiring immediate replacement and seven patients requiring two stents each to achieve success.[188] This is often concealed in the results as a higher number of SEMS placed than patients in the study, such as in a report by Bartelsman and colleagues, where 164 stents were placed in 153 patients despite quoted 100% success.[188,197] Kozarek and colleagues more accurately describe their technical failures in placing 56 SEMS in 50 patients; excluding operator error there was a 20% acute placement problem rate defined as immediate migration, dislodgement and perforation.[184] It is likely that the true value for technical success lies somewhere between 80 and 100%. In a similar fashion, studies rarely define what constitutes functional success, but it appears that over 90% gain some relief from dysphagia and that the quality of swallowed diet is good, with most able to manage semi-solids.[181,192,199,200] Relief of dysphagia is immediate, with patency maintained unless complications develop.[173,188,201–203] In a similar fashion to rigid tubes, SEMS are useful as salvage palliation following the failure of another therapy, although the placement of more than one stent may be required.[204]

Complications

Although initial studies quoted low morbidity, more recent studies cite migration, pain and incomplete expansion as significant problems.[189,197] Immediate migration is probably a result of technical failure, namely, poor placement, incomplete expansion, excessive dilatation or inappropriate stent type (*Table 3*).

Chest pain is common and occurs in 10–60% of patients after placement, 50% of whom require opiate analgesia.[179,187,188,207,208] Disabling pain is more common with the large diameter SEMS.[189,190] Although many series report no procedure-related perforations, they can and do occur in 4–7% of procedures. If recognised, these are best managed by immediate placement of an occluding stent (either a covered SEMS or a rigid tube).[173,181,188,189,193,197,203,206,209–211] Reflux oesophagitis occurs when stents are placed across

TABLE 3 *Early migration rates for SEMS*

SEMS	Early migration	References
Ultraflex	<2%	200, 210, 211
Wallstent	5–9%	195, 209
Gianturco Z-Stent	4–6%	176, 182, 195, 209

the gastro-oesophageal junction, and although proton-pump inhibitors limit morbidity, there remains a significant risk of aspiration pneumonia with any stent, especially in the presence of opiate analgesia, of between 3 and 9%.[173,181,197] Although insertion of stents is not usually considered for tumours close to cricopharyngeus because of foreign body sensation, three published series achieved a technical and functional success in 87.5–100% with proximally placed SEMS and only 20% foreign body sensation; however, most clinicians would avoid this risk if possible.[212–214]

Late complications leading to readmissions and reinterventions occur in 9–50% of patients.[148,173,189,195,215] Ingrowth was an early, major drawback of uncovered stents, but is now rarely seen, whereas overgrowth remains a problem in 6–8.5%, but is easily managed by ablative treatments or insertion of a further stent.[173,181,188,192,203] Food bolus obstruction occurs in 4–16%, less commonly than with rigid intubation owing to the greater internal diameter, and can be rapidly cleared endoscopically as an outpatient procedure.[181,182,188,189,192,200,216] Late migration occurs in 10–27% of covered SEMS, especially when placed across the gastro-oesophageal junction, although larger diameter stents may migrate less.[173,182,186–188,200,205,210,217] Procedure-related mortality lies somewhere between 0 and 8.5% owing to perforation, aspiration or haemorrhage.[179,182,187–189,192,194–197,209,218,219]

Specific stent complications

Tumour ingrowth was a problem with early, uncovered Wallstents, but the stent is now partially covered, which has reduced ingrowth at the expense of an increased migration rate of up to 25%. The exposed steel wire filaments at the ends of the stent have led to endoscope damage and there is a small risk of these wires perforating the oesophageal wall and damaging local structures such as the aorta.[148]

Ultraflex stents also suffered from ingrowth in 9–20% before they gained a covering sleeve.[192,220] Poor expansion in up to 40% means that some clinicians routinely advocate preinsertion dilatation to 15 mm and balloon dilatation postinsertion, but these practices may increase the migration rate.[71,148,181,196,221] The lower expansile force and greater flexibility of the ultraflex SEMS may be advantages when managing highly angulated tumours.

Z-Stents generally have a lower complication rate than other SEMS in published series. However, migration rates are high, especially in multicentre studies, and this has raised the problem of a learning curve for accurate Z-stent placement.

Additional treatment

Placement of a SEMS does not preclude any other treatment, and ablative treatments may be necessary to manage ingrowth or overgrowth and should be regarded as complementary rather than competitive.[50,220,222,223] Studies are equivocal as to whether additional radiotherapy or chemotherapy increases SEMS-related complications and mortality.[210,224–226] Placing a SEMS for recurrent disease after primary radiotherapy is associated with increased mortality, and tumour-shrinking radiotherapy post-SEMS may result in dislodgement of the stent or stent erosion in up to 33%.[173,212,227,228] Kinsman and colleagues demonstrated increased morbidity and mortality in a study of nine patients; eight (89%) had a life-threatening complication and the five patients who died as a result all had prior radiotherapy or chemotherapy.[188] Conversely, a recent retrospective study found no associated morbidity, although serious complication rates were higher in both groups than the literature norm.[179] One small, non-randomised study of SEMS plus chemoradiotherapy was associated with improved survival, but selection bias played a significant role.[229]

Summary

SEMS were introduced in the early 1990s as an alternative to conventional therapies. They are based on the same principles as rigid intubation, but made from a compressed flexible, metal mesh, which gently expands after deployment to full size over 24–48 hours. Like rigid tubes, SEMS promised rapid, effective and lasting dysphagia relief in a single endoscopic treatment session with lower morbidity and mortality because of the less traumatic insertion, and the larger diameter design was such that the quality of swallowing following placement should be improved to near normal. This would minimise hospital attendance and enable patients to return home quickly and remain at home during the terminal stage of their disease.[187,189] Early results were excellent and

SEMS rapidly supplanted conventional treatments in many institutions.[39,230,231] Unfortunately, the purchase cost for SEMS is high as they are hand-assembled, and the cost can escalate if more than one stent is necessary to bridge the tumour or if poor placement results in immediate restenting.[181,192,197,200,205,216,221,232–238] To recoup this expense, SEMS would need to be associated with faster hospital discharge, fewer complications and thus lower readmission and reintervention rates. Alternatively, they would offer more effective palliation for similar cost. Early comparative studies demonstrated lower morbidity and more effective dysphagia relief for SEMS treatment over rigid tubes, but none drew concrete conclusions owing to inherent design flaws. More recent evidence suggests that the improvement in dysphagia is not as great as expected and although early morbidity is low, late complication rates are high, thereby negating early benefits. SEMS are also difficult to move or remove once deployed, so placement must be meticulous to ensure effective palliation and reduce migration. To date, no accurate cost-analysis study has been performed upon which practice could be based. Again, the problem of evaluating the effectiveness of palliation is limited by the research that has been performed, with many series including patients with extrinsic compression and recurrence following curative surgery, making extrapolation to primary palliation difficult.[173]

Current developmental design is centred on plastic expandable stents with associated reduced manufacturing costs. One design is expanded by balloon then hardened by ultraviolet light irradiation, and initial results are promising, with 100% technical and functional success and no procedure-related complications.[239] It is likely that plastic-based SEMS will be developed further and there is even the prospect of regenerative oesophageal tissue-lined stents, but these are some way off production.[240]

Comparative studies

Performing a balanced, prospective, randomised study is difficult in a palliative population. Randomisation itself may be deemed unethical in terminal patients, thereby compromising recruitment, and there are significant methodological issues owing to high attrition rates. Doctors may be unwilling to enter patients if one treatment has advantages over another in cases of specific tumour, patient and clinical characteristics, so that randomisation would be inappropriate. Many patients are unwilling to take part in any research, especially a study that necessitates confronting quality of life issues, and there are considerable difficulties in collecting data from patients who are ill and facing death.[241] It has been questioned whether randomised trials are practicable at all for the evaluation of palliative care and associated therapies.[242,243] As a consequence, comparative studies between treatments in inoperable oesophageal cancer are predominantly non-randomised and retrospective. This is further complicated in many studies by the use of a combination of therapies to achieve effective palliation, which makes interpretation of results impossible. Nor is there a definition of what actually constitutes good palliation and even though relief of dysphagia is important, some inoperable patients are untroubled by their swallowing and some are too unwell to warrant any intervention regardless of dysphagia status; as such, few studies include dysphagia grade or assess quality of life changes.

Oesophageal cancer also affects a heterogeneous patient group: both fit, young patients with metastatic disease and elderly patients with early cancers, but who are unfit for the rigours of potentially curative surgery. The natural history of the disease in these groups therefore varies enormously, with the dysphagia from an advanced, aggressive cancer recurring rapidly despite effective treatment. Psychosocial outlook and quality of life effects also vary widely between these generation-separated cohorts, with young patients more willing to accept life at any cost rather than a terminal state.

Deep-rooted fears and traditional teaching of the natural history of oesophageal cancer mean that some patients are never even referred for treatment, instead receiving palliative care and support from their GP and community primary care team. Since so many anatomical and pathological process boundaries are crossed by the disease, patients may be referred to any number of different physician groups, including medical gastroenterologists, surgical gastroenterologists, cardiothoracic surgeons, oncologists or geriatricians, all of whom bring their own preconceptions and treatment preferences to bear. Investment in and development of a palliative care expertise or a preference for a particular technique entails that any evidence of the superiority of one treatment over another could simply reflect the experience of the clinicians involved rather than the quality of the technique itself.[244]

As a result, the evidence for best palliation is limited. To date, despite the number of these

TABLE 4 *RCTs of SEMS versus rigid tubes in palliation*

Reference	*n*	SEMS	Rigid tube	Dysphagia	Morbidity
Knyrim *et al.*, 1993[180]	42	Wallstent (uncovered)	Wilson Cook	No difference	Tube worse
De Palma *et al.*, 1996[183]	39	Ultraflex (uncovered)	Wilson Cook	No difference	Tube worse
Siersema *et al.*, 1998[248]	75	Gianturco (covered)	Medoc Celestin	No difference	Tube worse
Roseveare *et al.*, 1998[245]	31	Gianturco (covered)	Atkinson	Tube worse	No difference
Sanyika *et al.*, 1999[201]	40	Wallstent (covered)	Procter Livingstone	Tube worse	Tube worse
O'Donnell *et al.*, 2002[249]	50	Wallstent (covered)	Wilson Cook	No difference	No difference

studies, no one treatment has been shown to be substantially superior to any other.

SEMS

Comparison with rigid tubes

SEMS were developed to have important advantages over conventional rigid tubes. They have a larger available lumen, thought to improve the quality of swallowing, and a less traumatic insertion technique, claimed to reduce procedure-related morbidity and mortality.[245,246] However, SEMS have a high purchase cost, approximately ten times that of the rigid tubes, and although they are associated with a low early complication rate this is tempered by a high late reintervention rate due to ingrowth when uncovered and migration when covered.[247] SEMS are one of the few areas of palliative treatment in oesophageal cancer that has been studied in depth. Six RCTs have been performed that directly compare SEMS to rigid intubation (*Table 4*).

From these studies it appears that SEMS are associated with less morbidity and more effective dysphagia relief. However, all of these studies had significant design flaws. Knyrim and colleagues demonstrated that the extra SEMS purchasing cost was offset by reduced complications and reinterventions. However, the study was small (n = 42), with an insertion technique that biased the results in favour of SEMS; SEMS were inserted under sedation with a maximum predilatation of 10 mm, whereas rigid tubes were placed under general anaesthetic after universal 20-mm predilatation. As a result, no complications were seen with SEMS, whereas intubation-related mortality was 14% (n = 3). Since the cost analysis was based on avoidance of death and length of hospital stay, this was similarly biased; however, there were no differences in functional success or survival between the groups.[180] In a similar study, De Palma and colleagues again demonstrated no functional differences between the treatments, but major differences in mortality and morbidity. In this study, SEMS patients had zero morbidity and mortality versus 21% morbidity and 15.8% mortality with rigid tubes, but this was again biased by aggressive dilatation to 20 mm for intubation compared with only 10–12 mm for SEMS.[183] Siersema and colleagues performed a larger, more complex study (n = 75) and reached the same conclusions, but with similar bias towards SEMS. Some of the patients also received radiotherapy and/or chemotherapy before stenting, which corrupted the results by increasing the risk of device-related complications per se.[248] Sanyika and colleagues again demonstrated better dysphagia relief with SEMS, but concluded that these were 1.9 times more expensive to implant and accurate placement was essential to prevent associated complications.[201] Roseveare and O'Donnell's studies attempted to counter previous research deficiencies by using comparable sedation and insertion techniques for both treatments.[245,249] Complication rates were now shown to be equivalent between treatments in both studies, implying that insertion techniques had been accountable for the differences seen in the preceding research. However, in Roseveare and colleagues' work SEMS were associated with better dysphagia relief and SEMS-treated patients maintained their weight longer, enjoyed food more, survived longer and were discharged from hospital earlier.[245] This was reflected in a cost benefit for SEMS as long as the cost of an overnight hospital stay exceeded £120 per day. However, this study has been criticised for being too small (n = 31), with participants spread between three different hospitals, and for using an old rigid tube design (Atkinson). The quality of life analysis was basic and the economic evaluation based only on initial stay, not subsequent service use, thereby omitting the problem of SEMS-related late interventions.[245] The more recent research by O'Donnell and colleagues was an informed pilot study (n = 50) which included quality of life and survival elements as well as a comprehensive cost analysis extending past the initial procedure and related hospital stay to cover later reintervention resource use. This demonstrated no statistically significant differences in effect or cost between the two therapies.[249]

Non-randomised studies have demonstrated similarly inconclusive findings. Taal and colleagues, in a retrospective analysis of 132 consecutive patients, demonstrated comparable technical success for SEMS and rigid intubation, but better functional success, lower morbidity and lower mortality with SEMS.[250] Davies and colleagues found comparable complication and mortality rates, but a higher perforation rate with rigid intubation leading to a longer hospital stay (median 10 days versus 3 days, $p < 0.01$).[191] Kozarek and colleagues retrospectively compared 47 patients with rigid prostheses to 38 treated with SEMS. Early complications, dysphagia scores and fistula occlusion rates were comparable, but intriguingly, subacute complications were more common with SEMS (60% versus 80%, respectively).[184]

In summary, there is no conclusive proof that SEMS are any better than rigid intubation in terms of dysphagia relief. Complication rates cannot be interpreted without caution owing to differing insertion techniques, and no cost analysis has been performed upon which practice could be based.

Comparison with laser

Adam and colleagues have performed the only prospective RCT of laser therapy versus SEMS treatments, demonstrating substantially better functional success with SEMS, but few other differences.[251] However, Gevers and colleagues, in a non-randomised, retrospective review of 125 patients treated by laser therapy ($n = 70$), plastic endoprosthesis ($n = 34$) and SEMS ($n = 21$), demonstrated no differences in the reduction of mean dysphagia score between groups, but significantly more common complications in stent-treated patients.[252]

Comparison of SEMS with SEMS

Covered versus uncovered SEMS

In a non-randomised study, Ell and colleagues found that covered Wallstents migrated less frequently than uncovered Wallstents and suffered less from tumour ingrowth.[203] However, in a prospective, randomised comparison, Adam and colleagues demonstrated an equivalent reintervention rate, with 26% of covered stents migrating and 26% of uncovered stents developing ingrowth.[251] More recently, Vakil and colleagues performed an RCT in 62 patients, with higher reintervention rates in the uncovered stent group due to ingrowth (27% vs 0%, $p = 0.002$).[253] (259) As a result of these studies, most clinicians now favour covered SEMS.

SEMS designs

Dorta and colleagues compared uncovered Wallstents and Ultraflex SEMS retrospectively and reported better functional effects and significantly fewer reinterventions with Wallstents.[221] In contrast, Schmassmann and colleagues showed that uncovered Wallstents were associated with worse mortality, early complication rates and pain, but with less late stent dysfunction, reinterventions and costs than Ultraflex SEMS.[189] More recently, Siersema and colleagues randomised 100 patients to covered Ultraflex, Flamingo Wallstents and Gianturco-Z SEMS, all treatments relieving dysphagia equally with no statistically significant difference in the complications observed.[254]

Laser

Comparison with rigid tubes

In a retrospective study, Buset and colleagues demonstrated comparable functional success with intubation and laser palliation, but morbidity and mortality were higher in intubated patients (13.8% versus 3.6% and 4.3% versus 0%, respectively).[255] In a prospective, non-randomised study of 73 patients, Loizou and colleagues again demonstrated a lower perforation rate with laser treatment with no treatment-related deaths (2% versus 13%, $p < 0.02$), but that laser patients required more procedures (4.6 versus 1.4, $p < 0.05$) and more days in the hospital (14 versus 9, $p < 0.05$) to achieve equivalent dysphagia relief.[4] Alderson and Wright, in a randomised study, also demonstrated significantly more interventions and longer hospital stay for laser therapy, but it was ultimately associated with a better quality of swallowing.[256] This is a common finding, with Carter and colleagues in another study noting that 33% of laser patients could manage a solid diet compared with only 11% of intubated patients ($p < 0.05$), but Loizou and colleagues noted that between laser treatment sessions the grade of dysphagia fluctuates more than with a rigid tube.[4,244] Sculpher and colleagues found significant cost advantages for intubation over laser treatment.[257]

Comparison with dilatation

An interesting study by Anand and colleagues compared dilatation versus laser therapy for patients undergoing palliative chemoradiotherapy and demonstrated no difference in dysphagia relief or quality of life, suggesting that much of the dysphagia-relieving effect of laser treatment may be due to pretreatment dilatation.[258]

Comparison with APC

To date there have been no studies comparing APC and other palliative modalities, but it appears from observational research that the quality of APC palliation is comparable to laser therapy.[65,66,70,149]

Comparison with PDT

In a prospective, randomised, multicentre study of 236 patients the improvement in dysphagia for PDT and laser was equivalent, but serious complications were higher in the laser group (perforation rate 7% versus 1%, $p < 0.05$) and led to termination of treatment in 19% versus 3% ($p < 0.05$). However, minor but debilitating side-effects were extremely common with PDT.[81]

Comparison with ETN

Carazzone and colleagues performed a prospective, randomised comparison of ETN versus laser therapy, with similar dysphagia improvement and dysphagia-free intervals between treatments, but 78% of ETN patients experienced distressing levels of pain.[259] Angelini and colleagues compared tumour injection of 3% polidocanol to laser in a prospective, randomised study, with equal effectiveness, but intratumoral injection was considerably cheaper.[260]

Laser combinations

Konigsrainer and colleagues published a prospective, randomised study of laser plus EBRT versus SEMS, but 44% of the SEMS-treated patients also received laser treatment. This is typical of a mixed treatment study, leading to difficulty in interpreting results. Both groups experienced improved dysphagia, but restenosis, severe and life-threatening complications, treatment-related mortality and hospital stay were all more common in the radiotherapy arm. There were no differences with regard to survival and cost was highest with radiotherapy.[261] Laser treatment alone has been compared to laser therapy augmented by radiotherapy in three prospective, randomised studies: two used EBRT and one intraluminal brachytherapy. Although the radiotherapy increased the dysphagia-free interval, it did not confer a survival benefit and it also resulted in greater morbidity, and as a result these patients ultimately required more endoscopic procedures rather than fewer.[262–264]

Chemotherapy

No comparative palliative therapy study has included a chemotherapy arm. Herskovic and colleagues performed a prospective study of chemoradiotherapy versus radiotherapy alone in potentially curable patients. This trial was stopped after the results in 121 patients demonstrated a significant survival advantage for those receiving chemoradiotherapy (median survival 12.5 months versus 8.9 months). However, severe and life-threatening side effects occurred in 64% of the combined therapy patients, compared with 28% of those treated with radiation alone.[91]

BICAP

BICAP was compared with laser therapy by Jensen and colleagues in a non-randomised, consecutive series, with comparable relief of dysphagia, but with greater numbers of serious complications in the BICAP group.[76] In a prospective, randomised comparison with rigid intubation, dysphagia relief was equivalent, but significantly more BICAP treatment sessions were required to maintain effective palliation.[74]

Palliative surgery

A prospective, randomised study ($n = 106$) comparing rigid intubation to palliative surgical bypass demonstrated comparable dysphagia relief for the two treatments but intubation was associated with significantly lower morbidity and mortality than surgery (9% versus 37% and 5.5% versus 7.8%, respectively).[265] Revisiting palliative surgery more recently in a retrospective study, Cantero and colleagues reported worse relief of dysphagia (76% versus 93%), with more complications (28% versus 0%) and a higher mortality (24% versus 6.6%) with palliative surgery than with SEMS.[266]

Cost-effectiveness

Only two RCTs of palliative therapies in oesophageal cancer have included a formal cost analysis. Knyrim and colleagues showed that Wallstents offset their initial purchase cost by a reduction in later reintervention costs, but flaws in the design of the study biased these results. Roseveare and colleagues demonstrated that the initial treatment cost with a Gianturco Z-stent was lower than that of an Atkinson tube if the cost of inpatient hospital stay exceeded £120 per day, but this study only concentrated on initial stay and did not take into account later treatment and reinterventions.[180,245] Nicholson and colleagues performed a retrospective cost-analysis study using non-randomised data and found that the average cost per patient treated by SEMS (mean £2817) was lower than that of conventional therapies including rigid intubation and radiotherapy (mean £4566), but that this was not significant, and when the data was adjusted for survival this difference was not so

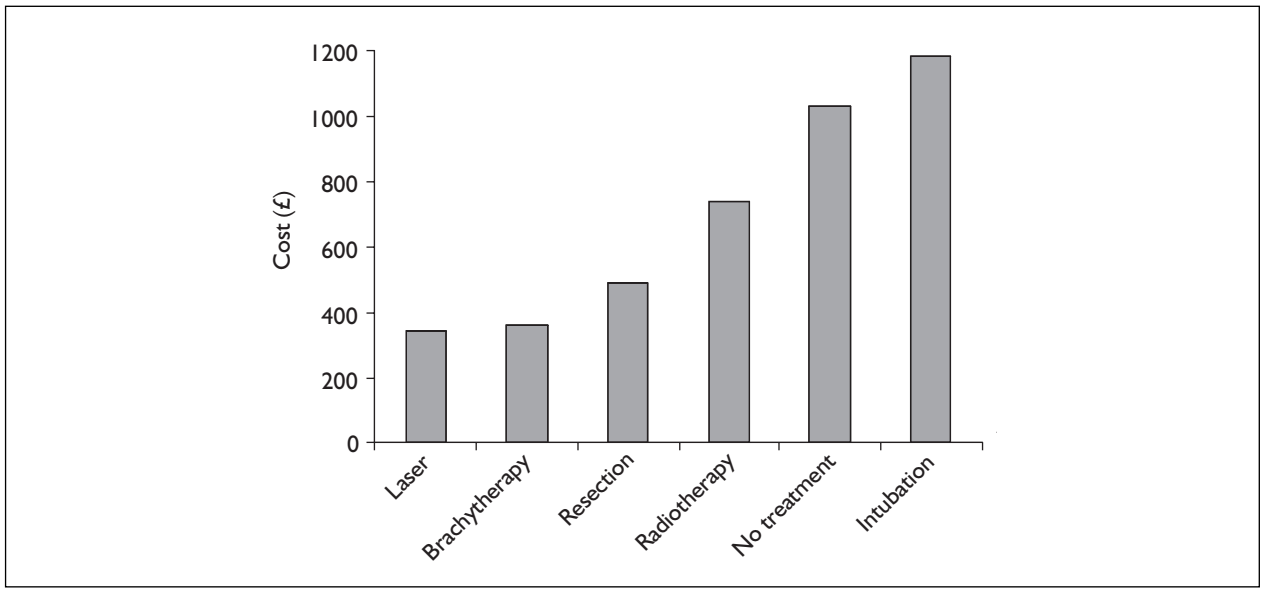

FIGURE 2 *Median cost of treatment per month of survival after treatment of oesophageal cancer by primary treatment modality (after Farndon and colleagues, 1998[241])*

marked (i.e. survival was worse for those palliated with SEMS).[246] Birch and colleagues also undertook a retrospective cost analysis of SEMS versus Atkinson tubes, with significantly more complications and a longer hospital stay for intubated patients, and as a consequence the median total cost of hospital stay was £1745 for SEMS versus £2349 for tubes (not significant), but both stent treatments were inserted under general anaesthetic, which is unusual.[267] Farndon and colleagues performed a comprehensive economic evaluation of patients with oesophageal cancer, assessing quality of life data prospectively in 51 patients and allying this information to retrospective clinical data collected from 139 patients (77% of whom had undergone palliation) to calculate a crude cost-effectiveness ratio of median cost of treatment per month of survival (*Figure 2*). Non-stent treatments such as laser and brachytherapy compared favourably to rigid intubation, but this study was primarily concerned with comparing the cost of curative surgery versus palliation and these findings were secondary extrapolations from the data.[241]

Summary

To date, cost-analysis studies have been based on initial hospital stay and initial purchasing costs, with no adjustments for quality of life, quantity of life or late interventions. A prospective study incorporating clinical data collection, with quality of life assessments and accurate cost analysis in the setting of a randomised controlled clinical trial was overdue.

Chapter 2

Patients and methods: main trial

Objectives

Primary

- To compare whether treatment with SEMS is more cost-effective in terms of resources consumed by the NHS than intubation with a rigid tube or conventional non-stenting endoscopic palliative treatment modalities in patients with inoperable oesophageal cancer.

Secondary

- To determine whether SEMS provide a better quality of swallowing compared with rigid intubation and other forms of conventional palliative treatment.
- To determine whether patients treated with SEMS require fewer follow-up interventions.
- To determine whether SEMS provide a greater number of quality-adjusted life-months.
- To determine quality of life effects associated with all treatment and health outcomes.

Study design

A multicentre pragmatic RCT with health economic analysis was conducted. The main hypothesis was that patients randomised to receiving SEMS would have better outcomes than patients randomised to non-SEMS treatments.

The study had two treatment arms: experimental therapy, and control therapy, each of which was further divided into two, so that there were four potential treatment groups (*Figure 3*). The two experimental treatments were both SEMS, identical except for their internal diameter: 18 mm and 24 mm. The control arm treatments were all non-SEMS treatments. Rigid intubation made up one limb of the control treatments, and all other non-stent modalities that the study centres performed, such as APC and radiotherapy, were included in the fourth limb. A secondary randomisation process ensured that treatment bias could not be introduced by trial clinicians; as such, once allocated to a treatment, patients remained in that treatment group unless treatment failure occurred. Failure of treatment was defined as 'recurrence of dysphagia such that further similar treatment is no longer deemed clinically appropriate'. Further stenting was inappropriate should a stent treatment fail and clinician discretion could therefore be applied to decide on the most pragmatic, 'best', further management. However, should a non-stent treatment fail and further non-stent treatment was not possible or indicated then secondary randomisation took place to one of the three stent treatments. Secondary randomisation was only allowed after discussion with the clinical fellow attached to the study to ensure that clinicians were unable to manipulate the randomisation process to give a treatment of their choice. Comparative analysis was on an intention-to-treat basis, so that patients nominally remained in their original study arm regardless of subsequent therapies and rerandomisation.

Ethics and confidentiality

The study was performed in accordance with the current version of the Declaration of Helsinki and was approved subject to minor amendments by the Multicentre Research and Ethics Committee (MREC) on 11 September 1998 with full approval on 8 October 1998 (MREC/98/3/51). Local ethical approval was also required from all study centres, primarily for the design and wording of consent forms and information sheets. All were approved before the study started.

Three amendments to the protocol were sought from MREC during the course of the study:

- an additional quality of life assessment at week 3: approved 11 May 1999
- health state utilities study consent form and information sheet: approved 13 July 1999
- concurrent acute-phase response study run on some participants: approved 19 June 2000.

Confidentiality

All personnel adhered to the code of practice as laid out in the Data Protection Act 1998. Patient medical information obtained as a result of the study was considered confidential and disclosure to parties other than trial personnel was prohibited. A patient identification code was used on forms that corresponded to computer-stored data further to ensure confidentiality of this information.

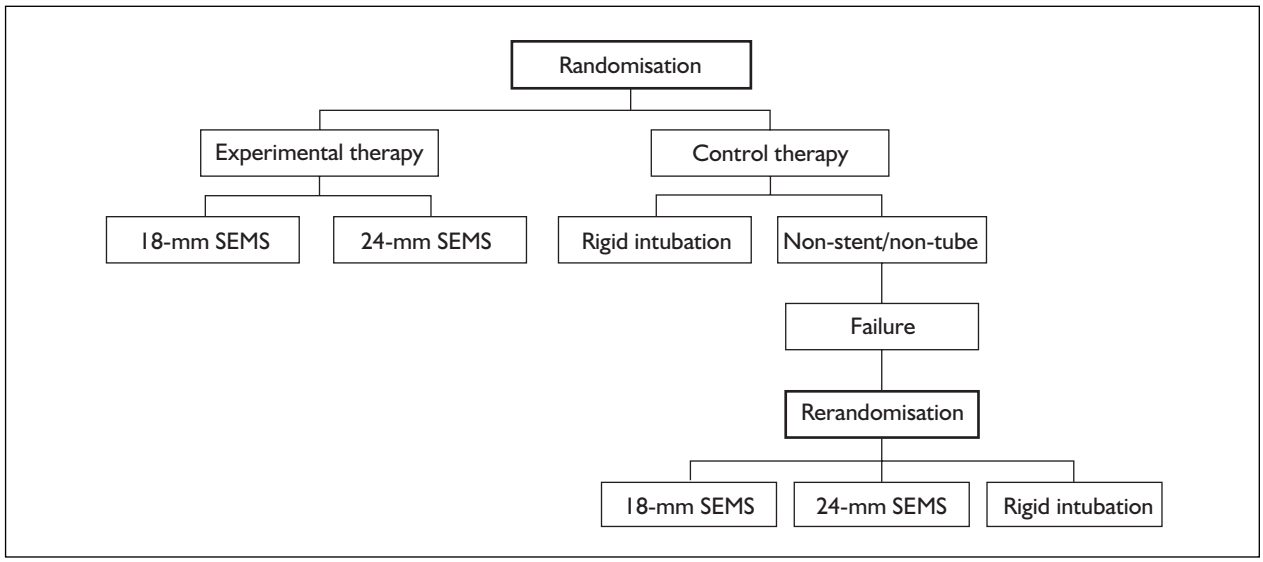

FIGURE 3 *Study design flowchart*

Consent

Suitable patients were asked to participate in the study on a voluntary basis. Written and verbal information was supplied with time to ask questions and at least 48 hours to decide whether or not to participate. Patients were informed that they could withdraw at any time without their medical care being affected and written consent was obtained. Although patients who withdrew from the study were no longer subject to assessment, survival data were still collected for these patients.

Outcomes in palliation

To determine what constitutes an 'ideal' treatment and judge different therapies it is necessary to define which outcomes are the most important. From the findings of previous studies it appears that the factors that make up a successful outcome in palliation are varied, diverse and inter-relational, and that no one single aspect determines effectiveness. Patient factors are paramount, but these are especially complex in terminal care. Although symptom relief is a priority, useful treatments may have a deprecatory effect on quality of life that outweighs the relief garnered in patients with a short lifespan. For example, effective cytotoxic chemotherapy may be unfavourable if a precious survival benefit is spent suffering intractable nausea, vomiting, hair loss and mouth ulcers.[268] Marginal survival benefits from extreme treatment regimens often receive widespread publicity, while the physical, psychological and social implications of treatment are overlooked: objective 'quantity' of survival being preferred to subjective 'quality' of survival.[2,142,269] A review by Gelfand and Finley in 1994 revealed that only 0.58% of oesophageal cancer publications dealt with quality of life issues.[270] Yet, when patients are given full information regarding the benefits and side-effects of radical treatments they are often unwilling to accept a 'life at any cost' attitude.[268,271] As a result, objective outcomes such as mortality, morbidity and cure may not be representative of effective palliation; indeed, WHO defines health as "physical, mental and social well-being and not merely an absence of disease or infirmity". Survival is still important in palliation, but more as a non-hastening of death by treatment than an actual survival benefit. No significant survival advantages have been conclusively demonstrated between the current palliative therapy modalities and, since the outcome is poor in lifespan terms, other measures should be considered that take into account the broader effects of illness and treatment.

Dysphagia

Dysphagia is the single, most burdensome symptom of oesophageal cancer, with dramatic effects on quality and quantity of life. It affects 70% of patients presenting with oesophageal cancer and is almost invariably present in advanced disease. Dysphagia is the most important of the symptom-related outcomes and a rapid and lasting improvement in swallowing ability is the primary objective of treatment. Dysphagia is quantifiable so that palliative treatments can be readily compared in their

TABLE 5 *Dysphagia grading*

Dysphagia grade	Swallowing ability	Diet
0: No dysphagia	No difficulties	Normal
1: Dysphagia to solids	Difficulties with solids	Soft
2: Dysphagia to semi-solids	Unable to swallow solids	Liquidised/puréed
3: Dysphagia to liquids	Difficulties with liquids	Liquids only
4: Total dysphagia	Absolute inability to swallow	No intake

effectiveness in this regard. It is usually graded on a simple five-point scale (*Table 5*). Assessment can be done by the patient or by a proxy, a carer or relative, or by medical staff.[273]

Technical dysphagia relief is not always associated with functional relief. Technical success is defined as the ability to restore luminal patency without complication or failure, generally equating to the ability to pass an 11-mm diameter endoscope through the stricture after treatment. Functional success is when treatment is accompanied by the ability of the patient to sustain oral nutrition post-treatment. The ultimate palliative treatment would have a 100% technical success rate (i.e. all patients treated would have a successful relief of mechanical obstruction) and achieve 100% functional effect (i.e. all treatments would relieve the feeling of dysphagia). However, relieving mechanical obstruction may not improve psychological anorexia or oesophageal dysmotility, and if the treatment itself is onerous and unbearable or the length of time spent in hospital receiving therapy is unacceptable then the subsequent effect on quality of life may be minimal. Equally, a technical failure can rarely be associated with considerable functional relief, thereby implying a significant psychological component to dysphagia.

There is currently no evidence base as to what constitutes an 'ideal' dysphagia-relieving treatment and although common sense would dictate certain parameters, until evidence is available these remain suppositions. It would appear sensible that treatments should be simple, uncomplicated and undemanding to perform with a shallow learning curve that is easy to become skilled at, as reducing operator dependence may increase consistency of results. There is some evidence to suggest that patients prefer a quick procedure, leading to rapid if not immediate dysphagia relief in the minimum number of therapeutic sessions, ideally one.[37,41] All tumour types would respond equally to this treatment and the associated morbidity and mortality should be negligible. It should be well tolerated and have a long-lasting effect. Symptomatic recurrence should be easily manageable by a repeat of the treatment, and other palliative treatment modalities should not interact unless these do so advantageously. The treatment should be readily available at a low cost in all hospital centres, with a minimal need for specialist equipment or staff training.

The 'ideal' palliative treatment of malignant dysphagia

- simple, straightforward, undemanding and uncomplicated
- shallow learning curve
- minimally operator dependent
- quick to carry out
- rapid, effective relief of dysphagia
- minimum number of therapeutic sessions
- negligible morbidity and mortality
- repeated treatments allowed for
- no interactions with other treatments
- low cost: initial and running
- minimal need for specialist equipment or staff training
- safe.

Quality of life

The concept of quality of life is highly applicable to the monitoring of treatments in a palliative care setting, but suffers from having no universally accepted definition and being poorly understood by clinicians. A commonly used definition is that of Schipper and colleagues, who suggested that "quality of life represents the functional effect of an illness and its consequent therapy upon a patient, as perceived by a patient".[273] The problem with the clinical application of quality of life is that these patient-perceived problems may be far removed from clinical issues and lose relevance for clinicians. Health-related quality of life instruments have been developed that encompass both clinical and patient-related elements, measuring a complex amalgam of physical, psychological and social well-being factors as well as 'global' quality of life or health assessments. To minimise confusion in this study, quality of life is taken to mean health-related quality of life. It is increasingly acknowledged that

quality of life best reflects the impact of treatment benefits in patients who have a limited life expectancy and can aid decision-making.[274] Furthermore, Blazeby and colleagues demonstrated that in oesophageal cancer patients certain quality of life domains may have significant prognostic implications and a role in the future for predicting those who are suitable for the rigours of radical surgery.[38]

Many quality of life instruments are available that outline the psychosocial impact of disease and treatment, and by using an appropriate instrument, clinically meaningful outcome measures can be ascertained. These instruments should be reliable, valid and sensitive to change, easy to comprehend and use, and not take long to complete, and the questions should be appropriate for the health problem in question and the likely effects of the therapy involved,[275] each of these measures being judged on the different psychometric proportion for quality of life scales. Since the concept of quality of life is difficult to define it is no wonder that despite several being developed there is no single instrument that is suitable to all clinical situations, and as such the following instruments were chosen for the study.

Karnofsky Performance Status scale

The Karnofsky Performance Status (KPS) scale was developed as a tool to assess the health status of patients undergoing palliative chemotherapy for primary lung cancer.[276] It was the first formal quality of life tool, was widely adopted in cancer-related illness and remains one of the most widely used generic scoring systems. However, the frequency of usage does not necessarily mean that this is an appropriate or accurate quality of life tool.[268] KPS measures performance status as defined by the ability to carry on normal activity and dependence on help or nursing care, and takes the form of a clinician rated 11-point ordinal scale from 0 to 100 in steps of 10, expressed as a percentage, where 100% equates to normal performance with no evidence of disease and 0% denotes death.[276] The scale has been criticised for three reasons. First, the scoring system places undue importance on physical functioning; for instance, a happy, well-adjusted and socially supported, paraplegic patient can score no higher than 40%, whereas an unsupported, emotionally crippled, depressed but medically well, patient with breast cancer will score 80–90%. Second, it takes no account of pretreatment ability, so that a fit, active, extroverted young patient who undergoes a leg amputation may score identically to a previously medically unwell, housebound elderly patient who undergoes the same procedure, despite the massive relative difference in quality of life change. Finally, it is a subjective, observational scale filled in by proxy by medical or paramedical staff, and as such is open to bias, wide inter-rater variability and low reliability.[277,278] Despite these deficiencies it remains the most commonly used assessment tool and as such was included in this trial, primarily to allow comparisons with previous studies.

The QL index

The Spitzer QL index is another quality of life tool developed specifically for use in cancer patients. It was designed to be concise, simple and quick to use, giving a generic score for a broad range of quality of life dimensions.[279] Considerable fieldwork with patients, clinicians and lay people led to the development of five items, each rated on to a three-point scale (0–2): activity, daily living, health, support and outlook on life. The maximum score is 10 and the minimum is 0. It is well-validated with much improved inter-rater and patient–doctor correlations compared with the KPS.[277] This reliability allows it to be used by different personnel at different times.[3,268] Drawbacks relate to the simple design, as there are many aspects of quality of life that are neglected by being grouped together into one item; for instance, the item 'daily living' includes problems with eating, washing, toileting, dressing, using public transport or driving a car. As a result, a housebound patient who is able to care well for themselves may rate the same as someone with toileting problems who is still able to drive. The system has also been criticised for item weighting. These are both inherent and recurring problems with all quality of life questionnaires in that it is difficult to determine the relative importance of differing quality of life aspects. As such, they are frequently grouped together or given the same weight or importance. Nevertheless, the QL index is a quick, simple and reliable tool that is likely to overtake KPS as the new baseline quality of life instrument, and has been included in this study for these reasons.[268]

EuroQol (EQ-5D)

EuroQol was designed to complement other quality of life measures, but the main value in relation to the present study is the ability to use the EQ-5D to generate a cardinal index of health for use in economic evaluations.[280] It takes the form of a self-completed, five-dimensional health state questionnaire that is similar in structure,

domains and questions to the QL index. A total of 243 possible health states can be generated, which can then be valued by comparing them with tariffs elicited from the general population. These data are readily available and do not need to be collected afresh. EQ-5D is well validated, reliable and responsive to change.[281] It was included for the economic analysis and for comparison with the QL index, EuroQol being self-completed and the QL index proxy completed by the research staff.

European Organisation for Research and Treatment of Cancer QLQ C-30

The European Organisation for Research and Treatment of Cancer (EORTC) generic cancer questionnaire QLQ C-30 is rapidly becoming a benchmark in quality of life assessment.[282] It was devised as a modular assessment tool with a core questionnaire and supplementary disease-specific modules. Five functional scales: physical, role, cognitive, emotional and social; three symptoms scales: fatigue, nausea/vomiting and pain; global health and quality of life scales and a few single important items assessing symptoms and financial impact of the disease are covered in the 30 categorical item core questionnaire.

Oesophageal cancer and quality of life

Stoller and colleagues were the first to apply a quality of life assessment in oesophageal cancer patients and found no differences in a retrospective comparison of quality of life in patients treated with radiotherapy or surgery.[283] Unfortunately, few investigators since have applied quality of life assessment in oesophageal cancer studies and those that have used poorly validated instruments. A review of publications under the subject heading 'esophageal neoplasms' using the MEDLINE database revealed a total of 18,763 articles from 1966 to date, and when combined with the subject heading 'quality of life' only 146 articles were identified in this same period (104 of which were in English) (*Table 6*). This equates to 0.55% of published research, unchanged since a similar literature review by Gelfand and Finley in 1994.[270]

A widely held belief is that dysphagia overwhelmingly influences quality of life.[41,142,161] Brunelli and colleagues confirmed this with the EORTC QLQ C-30 in 109 patients with malignant dysphagia due to advanced oesophageal cancer.[284] Loizou and colleagues also found a correlation between dysphagia and quality of life using the Spitzer QL index ($r = -0.43$, $p < 0.0001$) and a linear analogue quality of life scale ($r = -0.51$, $p < 0.0001$), and also demonstrated that relieving dysphagia improved quality of life.[285] However, work by the EORTC group demonstrated that although generic questionnaires such as QLQ C-30 were sensitive to gross quality of life differences, overall quality of life parameters correlated poorly with dysphagia and small differences between dysphagia-relieving treatments would not be detected if these questionnaires were used alone.[286] This was confirmed by van Knippenberg and colleagues, who adapted the Rotterdam Symptom Checklist to include a dysphagia scale ($r = 0.36$ preoperatively and 0.16 postoperatively), and by McLarty and colleagues, who demonstrated that although oesophagectomy affected functional outcome there was little correlation with quality of life scoring.[287,288] It appears that the proportional effect of dysphagia on quality of life is likely to be less than 15–20% using conventional questionnaires.[41]

TABLE 6 *MEDLINE search for quality of life in oesophageal cancer*

No.	MEDLINE search history	Results
1	Esophageal neoplasms	18,763
2	Quality of life	26,431
3	1 and 2	146
4	Limit 3 to English	104

As such, a disease-specific quality of life questionnaire was required to improve sensitivity and specificity. This would include further quality of life questions of relevance to this group of patients, as well as a dysphagia score. EORTC methodically developed a supplementary oesophageal cancer module, OES24, which included 24 unambiguous oesophageal questions to append to the generic QLQ C-30 questionnaire.[286] The additional material was selected from a large pool of potential issues generated from a literature search and interviews with oesophageal cancer patients, and by clinicians involved in oesophageal cancer patient care. OES24 has since been used in a number of studies, but is still undergoing validation.[38,241,289] Blazeby and colleagues demonstrated the sensitivity of the instrument for oesophageal cancer in 2000.[38]

Completion and compliance

EORTC QLQ C-30 and OES24 were designed to be self-completed to avoid observer bias and interobserver variation, and it is felt that only the patients can comment on their own physical and psychological status. However, poor patient

TABLE 7 *Palliative treatment costs*

Palliative modality	Cost per unit	Cost per treatment	Cost per course
Rigid tube	£105	£350	£2,450
SEMS	£825	£1,200	NA
Laser	£11,000	£350	£3,540
Intraluminal radiotherapy	£30,000	£1,112	£1,790
EBRT	£100,000+	£437	£1,237
Figures are approximate costs in pounds sterling (1998).[241]			

compliance is common, especially in elderly patients with terminal disease, and in oesophageal cancer studies compliance rates are quoted between 30 and 92%.[3,273,285,287] The use of a proxy to estimate quality of life is appealing, but although proxy ratings have been shown to be reliable and responsive to change, disagreements do occur, especially at intermediate values.[290] Further research by Blazeby and colleagues with the QLQ C-30 questionnaire demonstrated that proxy ratings were not sufficiently accurate and that this questionnaire should be self-completed with help from a trained interviewer only to clarify the format.[273]

Costs

If all the palliative treatments for oesophageal cancer were equally effective then a simple comparison of costs would suffice to determine the 'best' therapy, but this is not the case. As a result, it becomes necessary to determine the relative value in economic terms of the various treatment alternatives by systematically calculating and comparing costs and benefits. Many trials are concerned with treatment efficacy and costs are ignored; conversely, in an increasing number of studies costs are calculated without assessment of clinical outcome. By the identification of the most cost-effective treatment, economic analysis can help to allocate resources as long as more appropriate use of these resources will benefit the target population.

The fact that so many palliative treatment modalities exist for patients with oesophageal cancer is fuel for an economic study and yet, despite considerable cost implications, the burden to the health service of malignant disease and particularly palliation has received little attention.[241] This may be due to the inherent difficulties in performing studies in a palliative care setting, with a reluctance to conduct research in dying patients and clear ethical and methodological considerations to consider; for example, a high attrition rate owing to limited survival and low compliance rates owing to the physical and emotional burden of disease.[242,291] As a consequence, there are no reference costs for the palliation of inoperable oesophageal cancer in the UK, but extrapolating data from a previous study from the Newcastle unit in 1998, the overall cost to the NHS without taking into account community resource use is likely to exceed £20 million per annum.

The modalities currently available in the UK for palliation differ considerably in terms of initial purchasing cost and the cost of the day-to-day provision of the service (*Table 7*). However, most of these costs are exceeded by the cost of inpatient stay and the resources consumed by subsequent reintervention for complications of the treatment or recurrence of symptoms, that is, functional treatment failure. As a rule, patients who live longer cost more, as they are more likely to require reintervention and to use facilities. Many of the problems with previous cost-effectiveness studies lie in the focus on initial purchasing or 'trust' costs, with overall costs to the health service disregarded and no emphasis placed on length of survival or quality of life. The ideal palliative treatment then should be associated with minimal morbidity and mortality both at the time of treatment and post-treatment, so that readmissions and reinterventions are minimised. The interrelationships between palliative outcomes are most apparent in regard to complications as they have bearings on patient factors such as quality of life and symptom-free survival, but also on cost and resource use. The best reflection of morbidity is often resources consumed.

Economic evaluation

"Economics is the science concerned with the allocation of scarce means among competing ends."[292] Economic evaluation was developed to assist public sector investment planning by providing a framework for prioritising choices.

This allows a simultaneous evaluation of the costs and benefits of alternative therapies so that informed choice is possible. Measures of effectiveness in palliation are primarily relief of dysphagia, procedural morbidity and mortality, quality of life and length of survival, but these can be expressed in different ways such as pain-free or symptom-free days, complications avoided, improvement in mood or life-years gained. Each of these dimensions can be used to express effectiveness and allow a comparison between treatments in terms of marginal cost per unit of outcome.

Issues in the assessment of costs

The assessment of costs usually falls into two broad categories. First, there are costs directly related to the provision of the intervention. For metal stents, an immediate direct cost is the price associated with the purchase of the devices. Second, there are resources used as a result of changes in health status and healthcare. Examples are length of hospital stays and use of further treatments or services. Decisions about the measurement and valuation of such costs are often aided by the separation of costs into two elements: direct and indirect costs.

Direct costs refer to the resources consumed by a healthcare intervention and any associated events. These costs include those falling on the healthcare system and comprise items such as medical time, nursing time, drugs, equipment and supplies. Alternatively, implementation of an intervention may lead to costs incurred by patients and carers, for example, transportation to hospital.

Indirect costs refer to changes in the productive use of time by patients and others. The most important item in this category is the change in productivity as a result of changes in disability or life expectancy brought about by the healthcare intervention, for example, lost time from work. Other examples include changes in the amount of time available to pursue other activities, such as leisure.

Which costs to include depend on the research question and should embrace the perspective from which the analysis is conducted. The research question in this study was: relative to conventional care, does the introduction of SEMS for patients with inoperable oesophageal cancer lead to changes in healthcare costs and improvements in quality of life? As can be seen from the research question, the study was undertaken from the perspectives of both the healthcare system and patients. From the perspective of the NHS, direct healthcare costs were quantified using monetary values. Direct non-healthcare costs and indirect costs (e.g. travel time, caregiver time) were not measured in monetary values, partly because these costs were likely to be small in relation to healthcare costs, but also because it is difficult to estimate with any accuracy the additional time incurred, particularly with respect to caregiver time. Indirect costs were not quantified, partly because this group of patients would have already withdrawn from the workforce, while for carers, use of SEMS instead of non-SEMS treatments would be unlikely to lead to significant changes in work patterns. From the perspective of the patients, assessments included quality of life evaluation. However, there is an ongoing debate surrounding the question of whose values to use in the measurement and valuation of quality of life. As such, quality of life data were collected using both off-the-shelf questionnaires, from which general population-based values may be derived, and unstructured interviews, carried out to survey patient values of disease-specific health states.

The type of economic evaluation adopted

All economic evaluations have two common features. First, the costs of healthcare interventions are compared with their consequences. Second, an explicit comparison is made with at least one other alternative. In the context of new therapies, the alternative is usually conventional care. There are several of forms of economic evaluation, but for the purposes of this study, three are considered: cost–consequences analysis (CCA), cost-effectiveness analysis (CEA) and cost–utility analysis (CUA). These consider costs in exactly the same way, but differ in the way consequences are measured.

In CCA, consequences are assessed using an array of observable health outcomes, such as dysphagia levels, health status scores from measures such as the Karnofsky index and quality-adjusted life expectancy. The objective is to determine which treatment option produces significantly greater health benefits for significantly smaller costs, without the computation of cost/consequence ratios for all potential health outcomes. In CEA, however, only one health outcome is adopted in the primary analysis. For both CCA and CEA, if one option is significantly cheaper and produces significantly greater health benefits, that option is more cost-effective and dominates all other options. However, in CEA, if one treatment is associated with significantly greater improvements in health benefits and significantly greater costs

relative to another, examination of the incremental cost-effectiveness (C/E) ratio of the more beneficial but more expensive is usually undertaken. This shows the extra cost of achieving an extra unit of benefit. The ratio is defined as:

$$\text{C/E} = \frac{\text{Net costs}}{\text{Net effectiveness}}$$

where net costs and effectiveness are measured by the difference in costs and effectiveness between the more expensive healthcare intervention *A* and alternative *B*:

Net costs = Mean costs intervention *A* – Mean costs alternative B
Net effectiveness = Mean effectiveness intervention *A* – Mean effectiveness alternative *B*

CEA is most useful where there is one dimension along which consequences can be measured. However, it is often the case that healthcare interventions produce changes along several different dimensions. Moreover, interpretation of which intervention is more cost-effective becomes problematic in CCA where one intervention dominates another on some but not all consequences. In such a case, a judgement is required about the relative importance of different consequences.

Once diagnosed with cancer, patients face a barrage of information and medical terminology, as well as dealing with a terrifying social stigma. No matter how understanding and empathetic clinicians can be, it is the patient who endures the side-effects of treatment and an uncertain final outcome. It is unrealistic in terms of comprehension and emotional strength to expect all patients to participate in treatment decisions, especially in palliation where patients understand that they have only a limited lifespan and view this as a life-sentence. More often than not the decision falls on the clinician. It is therefore important that clinicians are aware of the preferences that patients may place on different treatments and on trade-offs that they are willing to undertake between quality of life, length of life and the side-effects of treatments. However, CCA and CEA neglect the views and preferences of the patients. Although this appears to be of paramount importance in the care of terminally ill patients it has never been addressed before in relation to the palliation of oesophageal cancer.

A model for decision-making in these situations can be derived from CUA, particularly where the primary purpose of healthcare interventions is improvement in quality of life. As with CCA and CEA, CUA aims to determine which alternative produces greater health benefit per pound spent. However, the main feature of CUA is the measurement of consequences in terms of values. Preferences are elicited, then used to build up values or utilities for a variety of health states. These values (*V*) act as units of well-being and in a single numerical value describe the degree of individual patient preference for particular health states or satisfaction of outcome, which can then be used to rank disease states and treatments. Utilities are traditionally based on a cardinal scale from zero to one, where 0 = least desirable and 1 = most desirable.

These values are combined with information on the duration of health states to calculate quality-adjusted life-years (QALYs). This is an integrated model of life-years adjusted by a measure of quality of life experienced during this time, such that 1 year of good health quality is equivalent to 2 years of half that health quality; that is, the value for the outcome state (*U*) is multiplied by the length that a person remains in that state (*T*) to give the expected QALYs ($U \times T$). These can be used to compare alternative therapies based on cost–utility (C/U)ratios and marginal costs per QALY gained.

The C/U ratio is given by:

$$\text{C/U} = \frac{\text{Net costs}}{\text{Net QALYs}}$$

where net costs and QALYs are defined as:

Net costs = Mean costs *A* – Mean costs *B*
Net QALYs = Mean QALYs *A* – Mean QALYs *B*

Owing to the inclusion of a broad range of health outcome measures, this report uses CCA as the main form of analysis; however, as the primary outcome measure in the economic evaluation is quality-adjusted life expectancy, CUA is also undertaken.

Patient preference elicitation

Various techniques have been developed to assign numerical utilities to potential patient health states. Preferences are usually elicited in face-to-face interviews using props and visual aids to help comprehension of concepts and facilitate measurements. All elicitation techniques use a series of previously ranked scenarios such as health states or the potential outcomes from

treatments, which are then assigned valuations. Time trade-off (TTO) and standard gamble (SG) are the most commonly used techniques. TTO is most appropriate then when trading length of life against the loss of quality of life and SG is most appropriate when there is a risk of an early death. It becomes difficult when these situations occur simultaneously, such as in the palliation of patients with inoperable oesophageal cancer.

Time trade-off

TTO was developed for use in healthcare decision-making by Torrance, and is most suitable when dealing with two certain options, such as a shorter life with a better quality versus a longer life with a lower quality.[293] This is the case in palliative therapies when a treatment has minimal survival gains for a significant side-effect profile. The subject is asked how much time (x) in a state of perfect health is equivalent to time (t) in another, by definition, worse health state. The score x/t is the TTO utility value and this proportion is assumed to be constant; that is, if 16 years in perfect health is considered to be equivalent to 20 years in an inferior health state then 12 years in perfect health is equivalent to 15 years in the same inferior health state. However, this may not be the case, especially when dealing with limited life expectancy such as in palliation and, furthermore, people with a longer life expectancy may trade proportionally more time off than those with short life expectancy.[294] As such, it is better to fix time t so that the willingness to trade time is more realistic; for example, in terms of palliative health states relating to oesophageal cancer, t may be fixed at 12 months, with time traded from this for the acquisition of perfect health.

TTO is considered to be difficult to use and relies on well-informed patients and experienced interviewers. Although TTO has been proposed as the best method to value the outcomes of palliative therapies there are doubts over feasibility when dealing with severely limited life expectancy such as experienced in oesophageal cancer patients and there is some evidence that standard gamble methods may be more acceptable to patients in these situations.[295,296]

Standard gamble

SG is most suitable for decisions where there is a risk of dying associated with the treatment choice. This has become the gold standard of utility assessment. The respondent is asked whether, in order to obtain perfect health, they are willing to accept a risk of immediate death. By varying the chances of death the respondent's point of indifference is obtained. This is the point at which the respondent is indifferent (i.e. cannot choose) between a certain health state and a gamble that will lead to either perfect health or immediate death.

Scenarios

Drawing up realistic and applicable health state scenarios is one of the most difficult aspects of utility analysis and accounts for the major drawback of elicitation techniques, framing. How information is interpreted depends not only on the background knowledge and experience of the respondent, but also on how this information is presented. Pre-existing beliefs account for major flaws in the elicitation of health state preferences. This was well demonstrated in an excellent study by McNeil and colleagues, where three groups of respondents (patients, physicians and business students) were asked to choose between two treatments for lung cancer.[271] Both naive and sophisticated subjects were influenced by the presentation of the data. All were biased against radiotherapy and for surgery when these were identified but not when only statistical information was presented to them. Also noted was that the probability of survival was preferred to the probability of death, even though they were identical. This represents a cognitive illusion.

Two approaches are used for drawing up scenarios: the decomposed or state scenario and the holistic or process scenario. In decomposed scenarios, each problem is broken down into separate dimensions, whereas the holistic approach considers all aspects of a treatment process simultaneously. For example, a state scenario would refer to a single moment in time at some point during or following treatment, with temporary side-effects or duration of the health state being ignored. In contrast, process scenarios describe a dynamic situation where temporary and permanent side-effects are taken into account as well as life expectancy and the probabilities of treatment outcomes. Both are drawn up after extensive literature review, structured and unstructured interviews with patients and the input of experienced clinicians. Process scenarios tend to be longer and more complex, and often contain sensitive and potentially disquieting information, which may overburden the respondent so that they only latch on to a few key phrases. The advantage of state scenarios is that they are short, and it is easier to comprehend, assimilate and compute the information given. Surprisingly, though, when compared in a patient

population, process scenarios are often preferred to state scenarios, with respondents appreciating the comprehensiveness of the descriptions.[296]

Patient group for health state valuation

There are many issues of the feasibility of utility theory studies in a palliative population, as patients may not be willing to contemplate the consequences of treatment and risk of immediate death as this is viewed as immediately threatening. Respondents are vulnerable and sensitive when discussing death and dying, let alone their own inevitable prognosis. Facing even hypothetical trade-offs between health and death is unreasonable and as such it is difficult to recruit patients. Studies also suffer from a high attrition rate as the research population succumb to their disease. Unfortunately, the use of an unaffected population rather than actual patients gives different utility measurements.[297,298] As such, a group of patients was identified who had received surgery for oesophageal cancer but whose status was currently rated as cancer free. These patients had intense familiarity with the choices between cancer care health treatments and had all experienced problems with swallowing. This is as close a group to the palliative population as was possible to use.

Rationale for choosing study treatments

The main research question was whether SEMS are a more effective form of palliation than other available palliative treatments (non-SEMS). Thus, the trial had two arms: an experimental arm comprising SEMS-treated patients and a control arm containing non-SEMS-treated patients.

Experimental therapy arm: SEMS

Two expandable stents were evaluated in the experimental study arm, differing only in diameter:

- covered self-expanding metal stent 1 (18-mm internal diameter Gianturco Z-Stent, Wilson-Cook Medical)
- covered self-expanding metal stent 2 (24-mm internal diameter Gianturco Z-Stent, Wilson-Cook Medical).

The 18-mm SEMS reflects current UK practice as this is the market leader. In addition, research to date has been based on the 18-mm SEMS, so that inclusion allows comparisons with previous studies. However, the largest diameter expandable stent on the UK market now has an internal diameter of 24-mm, offering an 80% (1.8 ×) increase in available cross-sectional luminal area over the 18-mm SEMS, which may affect the quality of swallowed diet. Given the normal oesophageal width, it is unlikely that greater diameter stents than this will be produced and as a result it was necessary to evaluate this stent. The only 24-mm internal diameter expandable stent on the UK market is the Gianturco Z-Stent, manufactured by Wilson-Cook. Available SEMS all differ in design, technique of insertion and expansion strength, so choosing two different design stents could lead to confusing and difficult to interpret results. As such, both the 18-mm and the 24-mm diameter SEMS chosen were Wilson-Cook Gianturco Z-Stents. Any outcome differences between the SEMS could only be attributed to the difference in diameter and not to design. The Gianturco Z-Stent is one of the most common stents in use in the UK, with comparable success to other stents and a similar morbidity profile, as demonstrated in previous studies.

Control therapy: non-SEMS

The control arm encompassed non-SEMS treatments. It was felt that this could also be broken down into two further subgroups:

- rigid oesophageal endoprostheses (Wilson-Cook Prosthesis, Wilson-Cook Medical)
- non-stent treatments (best available non-stent intervention appropriate to the nature of the tumour, including radiotherapy, thermal ablation techniques and ETN).

Rigid intubation had to be evaluated as this is the most commonly used treatment in the UK and thereby represents standard palliation. Four designs of rigid tube are available: Wilson-Cook, Atkinson, Celestin and Procter-Livingstone. The Wilson-Cook rigid endoprosthesis was chosen, as the majority of the study centres were familiar with this equipment and many felt that this reflected the latest evolution of the rigid tube. It is constructed from reinforced plastic with an external diameter of 16 mm for an internal diameter of 12 mm, and comes in lengths of 4.4, 6.4, 8.4, 10.4 and 12.4 cm.

The fourth group of the study and second control arm consisted of a variety of non-stent treatments chosen to reflect the expertise of the study centres. These techniques are not as universally applicable as intubation and stenting; for example, although laser therapy is well suited to treatment of a polypoid, exophytic tumour it is less well suited to dealing with diffuse, subepithelial disease. As such,

it was deemed appropriate that patients randomised to this arm should receive a modality that best addressed the characteristics of the tumour and the expertise of their local centre. This decision was left to the discretion of the study centre clinicians. Initially, all fourth arm treatments were endoscopic, including radiotherapy given as intraluminal brachytherapy; however, during the course of the study the clinicians responsible for the care of these patients felt that some would benefit most from EBRT and this was therefore added to this limb.

Trial management

Clinical management of patients entering the study was maintained by the collaborators in each study centre under the supervision of the centre lead consultant. A protocol for entering patients into the trial was agreed and piloted before the start of the study. Clinical information about patients assessed during the pilot phase and a sample of patients recruited to the study was assessed independently by clinicians from other centres to increase compliance to the protocol. Trial management was shared by the lead researcher and The School of Population and Health Sciences, Centre for Health Services Research (CHSR), University of Newcastle upon Tyne. A health economist from the centre was responsible for the measurement of health state utilities, collection of resource use data and the economic analysis for the trial, and a study statistician was appointed to ensure that randomisation adhered to protocol and for the analysis of data.

A clinical research fellow appointed to the study was responsible for the clinical components of the trial, including drawing up of protocols, obtaining ethical approval, providing day-to-day project management, the appointment and training of the research nurses, managing data collection and maintaining standards across all centres. The research fellow also ensured compliance to research protocol in the study centres, the development and production of data collection instruments, data entry, cleaning and validation, data analysis, and the preparation of reports and papers in collaboration with the other applicants.

The lead trial clinician had overall responsibility for the clinical management of the trial, with joint responsibility for the analysis and publication of trial results together with the lead project researcher with the CHSR, who also provided management of the project staff.

Research nurses performed the majority of patient assessments, introduced self-completed questionnaires to study patients, coordinated local clinical information retrieval and provided standardised information and assistance. To this end they received training and regular updated information from the clinical research fellow.

A project secretary/database manager was responsible for the production of data collection instruments, logging data returns, providing secretarial support to project staff, and production of reports and papers.

Collaborating centres

The study centres were selected to represent the diversity of interests of clinicians who treat oesophageal cancer patients and parallel the majority of UK hospitals in terms of facilities and staffing. Each centre was chosen on the merits of an interest in the palliation of patients with inoperable oesophageal cancer, together with established facilities for endoscopic intubation or SEMS insertion and proficiency in endoscopic, non-stent techniques. The centres agreed to standardise patient assessment and staging, as well as the techniques of palliation. Six centres were chosen initially, but owing to slow recruitment a further centre, Edinburgh, was added.

The Northern Oesophago-Gastric Unit (NOGU), Royal Victoria Infirmary, Newcastle upon Tyne (lead clinician: Professor SM Griffin; data manager: Mrs SM Davies)

The NOGU is a multidisciplinary regional centre specialising primarily in the surgical treatment of patients with upper gastrointestinal malignancy. The regional population is 3.3 million and the unit evaluates over 200 new patients a year. All modalities of palliative and curative treatment were available and there are close links to the Northern Centre for Cancer Treatment, an oncology specialist unit, with chemotherapy and radiotherapy services, and to the CHSR, a university-based unit with experience in multicentre patient-centred research. NOGU was the lead centre for the study and, in conjunction with the CHSR, was responsible for the management and running of the study.

The Cumberland Infirmary, Carlisle, (lead clinician: Mr SA Raimes)

The Cumberland Infirmary is another predominantly surgical, secondary and tertiary referral centre for oesophageal cancer with close clinical links to the NOGU. The unit sees 100 new patients with oesophageal cancer each year.

Considerable experience with rigid intubation was available at this unit and there was an oncology unit on site capable of delivering brachytherapy.

Bristol Royal Infirmary/Bristol Oncology Centre, Bristol (lead clinician: Professor D Alderson)
Bristol Royal Infirmary is an academic and clinical centre of excellence for the treatment of upper gastrointestinal malignancies serving a local population of 600,000, with a regional referral drainage population of 1.5 million to the Bristol Oncology Centre. The unit practises and has experience of all palliative modalities and is again a surgical centre. Although brachytherapy was not available at this centre, facilities were present for patients to travel to Portsmouth for treatment where necessary.

Royal Hampshire County Hospital, Winchester (lead clinician: Dr H Shepherd)
Royal Hampshire County Hospital is a district general hospital serving a local population of 220,000, but receives referrals from a wider area because of a special interest and expertise in the treatment of oesophageal cancer. The unit is a medical centre and has considerable experience in the design, evaluation and use of SEMS. Although laser/APC therapy and EBRT were not available on site, there were close links to Southampton General Hospital and brachytherapy was available in Portsmouth.

Southampton General Hospital, Southampton (lead clinician: Dr P Patel)
Southampton General Hospital is a large medical unit serving a local population of 500,000 and offers a broad range of treatment options for patients with oesophageal cancer. Considerable rigid intubation experience was available in this centre and facilities were made available at Portsmouth for cases requiring brachytherapy.

Queen Alexandra Hospital, Portsmouth (lead clinician: Dr P Goggin)
Queen Alexandra Hospital is another large medical unit which serves a population of 550,000. It offered a full range of expertise and facilities for treatment of patients with oesophageal cancer, including BICAP, stents, rigid tubes and brachytherapy.

Royal Infirmary Edinburgh & Western General Hospital, Edinburgh (lead clinicians: Mr S Paterson-Brown and Dr K Palmer)
The Lothian University Hospitals NHS Trust encompasses these two hospital bases, comprising a medical and a surgical unit, which act together as a large multidisciplinary centre draining a regional population of 800,000 from a catchment area of 700 square miles. All modalities of treatment and palliation were available, with considerable experience of endoscopic palliation.

The School of Population and Health Sciences, Centre for Health Services Research (CHSR) at the University of Newcastle (lead supervisor: Professor J Bond; health economist: Dr P McNamee; statistician: Dr N Steen)
The CHSR together with the NOGU provided the day-to-day management of the trial and was responsible for project management, the development of research protocols, the randomisation service, recruitment, training and management of research staff who were locally based but centrally managed, ensuring compliance to research protocol in the centres, the development and production of data collection instruments, data entry, cleaning and validation, data analysis, and the preparation of reports and papers, in collaboration with other applicants. The CHSR is a participating centre in the Medical Research Council Health Service Research Collaboration. It has a strong background in quality of life and outcome assessment work, service evaluation, managing multicentre studies and fieldwork, and collaborating with clinicians in different centres in the UK on various studies.

Patient selection

Inclusion criteria

A standardised, preoperative, tumour staging protocol was used by clinicians when recommending to offer or not offer surgical intervention. Patients were not offered surgery when the cancer had invaded beyond the wall of the oesophagus to involve adjacent structures, or had spread to surgically inaccessible lymph-node groups or to distant organs, or where their general physical health prohibited radical surgery. Patients with histological proven, previously untreated primary carcinoma of the oesophagus who were deemed unsuitable for a curative resection were then assessed for inclusion in the trial. Those who had undergone previous curative or palliative treatment were not eligible as this could only confuse the study outcomes. Since dysphagia relief was the primary outcome measure this had to be present with sufficient luminal obstruction to hold a stent or tube, defined as the inability to pass or hold firmly on an 11 mm diameter endoscope. At least 50% of the tumour had to lie within the oesophagus (i.e. Siewert type I or II oesophagogastric tumours were included).[299]

TABLE 8 *Eligibility criteria*

Inclusion criteria	Exclusion criteria
Primary carcinoma of the oesophagus	An aerodigestive fistula is present
50% of the tumour in the oesophagus	Malignant dysphagia is due to external compression or from a recurrence of a previously resected oesophageal cancer
Previously untreated (other than dilatation or open and close laparotomy)	The patient's health precludes the safe use of sedation for any procedure
Over 18 years of age	Tumour is histologically proven small cell carcinoma
Malignant dysphagia present with sufficient luminal obstruction to hold a stent or tube	Patient has had a laparotomy where a palliative treatment was instigated at the time of surgery
Unsuitable for curative resection	Tumour site necessitates placement of the upper limit of the stent or tube within 2 cm of the cricopharyngeus muscle
Signed informed consent	

To ensure ethical management all patients were over 18 years of age and able to give informed consent with interpreters used where necessary. The inclusion criteria are detailed in *Table 8*.

Exclusion criteria

Eligible patients satisfying the inclusion criteria were excluded if the malignant dysphagia was due to external compression or recurrence of previously resected disease, when an aerodigestive fistula was present or when stent placement would be within 2 cm of the cricopharyngeus, as these are situations where one palliative treatment may be favoured over another. Patients with small cell carcinoma of the oesophagus were also excluded, since the rapid, aggressive natural history of these tumours is not readily amenable to evaluation within a palliative study. Justifiably, all patients had to be able to tolerate sedation safely so that the procedures within the study could be carried out. These criteria are again detailed in the *Table 8*. The clinical characteristics of excluded patients were monitored and recorded throughout the study to ensure that there was no selection bias.

Allocation to treatment groups

Randomisation protocol

Potential study participants from the study centres were assessed to determine their eligibility for the trial using a flow-design entry form. Eligible patients could be referred to a single point for telephone randomisation during normal outpatient clinic hours (08.30 to 17.00 hours). This was managed by an independent member of the research team at the CHSR. Computer-generated block randomisation was used to allocate patients to one of the four study groups. Blocking the randomisation numbers within each centre ensured that approximately equal numbers of referrals were made to each arm of the trial throughout the period of the study, with an even spread of study treatments within the individual centres, thus helping to ensure that sufficient patient numbers would be achieved for comparative purposes. Study centres were issued with a personal identification code for the patient, together with a numeral coded treatment group. This was recorded on a randomisation form which, for the purposes of confidentiality, was the only documentation where the patient was identified by name. The randomisation service had close links to the clinical team in the Newcastle upon Tyne centre, so that any queries could be rapidly answered and dealt with to ensure that incorrect randomisation or abuse of the system was not possible. Where it was felt that there was a conflict of clinical interest these cases were immediately referred to the lead clinical fellow attached to the study. No secondary randomisation was allowed without discussion with the clinical fellow to ensure that no abuse of trust was made; thus, if a clinician was unhappy with the treatment to which the patient was randomised, it was not possible secondarily to randomise the patient to a more favourable or preferable treatment.

Sample size

The comparison of SEMS (experimental group) with non-SEMS (control group) therapies was the most important component of the trial. Based on projected power calculations it was proposed to recruit 120 patients into these two arms, that is, completed data for a total of 240 patients at the time of the first assessment at 6 weeks, and to allow for attrition due to withdrawals and early deaths of 20%, a total recruitment target of 300 was set. The study centres treated 530 patients

TABLE 9 *Assessment timetable*

	Time from entry					
Assessment	**Baseline**	**1 week**	**3 weeks**	**6 weeks**	**6+ weeks**	**Event**
Staging and entry	✓					
Consent form	✓					
Information sheet	✓					
GP information sheet	✓					
Randomisation form	✓					
Patient diary	✓			✓	✓	
Clinical evaluation	✓	✓		✓	✓	
Quality of life	✓	✓	✓	✓	✓	
Event form						✓

with oesophageal cancer in the 12 months preceding the study and the estimated annual palliative recruitment is 245 patients (Newcastle 40, Carlisle 20, Bristol 30, Winchester 45, Southampton 60, Portsmouth 50). As a result, the recruitment time was set at 16 months to allow for ineligibility and for a proportion of patients declining to participate.

Clinical assessment

A timetable for clinical assessment is shown in *Table 9*.

Once the outcomes measures and efficacy assessments had been defined these were incorporated into forms that were designed with ease of use and applicability in mind and to be used with a structured interview technique. The forms were intended to be complementary rather than competing, with a similar layout and feel. A pilot run using simulated patients helped to develop the forms into a user-friendly package. Midway through the study the event form underwent minor changes to improve and facilitate data retrieval. A flow chart was designed to facilitate patient entry into the study, which the individual centres could tailor to their specific use. Once a patient was identified as potentially suitable, a staging and entry form was completed. This form was also designed on a flow basis: completion of each page allows one to move on to the following page and thus ensured full completion and patient eligibility. This leads on to the completion of the randomisation form, which further stipulates entry criteria so that incorrect randomisation of patients to the study was minimised. At baseline and at regular intervals thereafter a clinical evaluation form was completed. As swallowing ability is the main outcome measure, this form contained a grading of dysphagia on the five-point standard scale. Quality of life assessments were made using the EORTC QLQ-30 questionnaire with disease-specific module, OES24, EuroQol EQ-5D, QL index and the KPS. A record of complications and survival was also made.

The quality of life and dysphagia assessments were made at baseline (on enrolment, before randomisation and treatment), 1 week after treatment and 6-weekly intervals thereafter until death. These measures are responsive to change and at this frequency of administration should allow estimation of the rate of change up to death. These evaluation questionnaires were designed to be completed as a standard, structured interview with the centre research nurses providing assistance and explanation, and this also allowed the nurse to make a clinical assessment (either in hospital or at the patient's home). If this was not possible then this was done by the clinician, depending on local practice. The quality of life questionnaires were self-completed and collected by hand, and patient notes were the basis of data on process of care. Data items reflecting important events – readmission to hospital, hospice care, retreatment, withdrawal or death – were extracted in a structured way and recorded prospectively on an event report form. Death in the community or hospice was recorded by seeking in advance the cooperation of GPs who informed the local clinician of this or other significant events outside hospital. Local death registers were consulted to check the date of death and copies of death certificates were obtained where possible.

Cost methods

The costs to the health service for each patient were identified and measured from the time of randomisation to death or study closure. Costs

accrued were calculated from prospective and retrospective resource use data. Resource use data associated with all treatments and procedures were collected by nurses from patient records. Within each centre, a dedicated research nurse was employed to record from patient records all interventions undertaken and all hospital visits (inpatient, outpatient and day-case care). Research nurses were informed by telephone or pager whenever a study patient was admitted to hospital. A coloured sticker placed on patient notes acted as a reminder to staff to notify the study team. To capture the nature of inpatient visits, the admitting speciality, number of admissions and length of stay data were recorded. For day-case and outpatient visits, the speciality and number of visits were recorded. All procedures and tests were recorded by type and frequency. These data were noted on event forms, which allowed for detailed collection. These included all resources used after randomisation, time spent in hospital as an inpatient and outpatient attendances and the department or ward attended, and resources use pretreatment, during treatment (staff time, materials, capital equipment) and post-treatment, that is, interventions undertaken as a result of complications (e.g. further endoscopy, medications). Medication use data, including the name, dosage and duration of each course of drug therapy, were gathered at assessments and at the time of any events. Community costs such as community hospice care, attendance or call-out of GPs and use of social services and paramedical staff were obtained every 6 weeks, with patients being allocated a diary to help in the collection of these data.

These data were then linked to obtained cost estimates. Two endoscopy resource survey questionnaires were sent to clinicians at each participating hospital: one to the medical gastroenterology department and one to the surgical gastroenterology department. This was conducted to identify the resources used during work-up before treatment and during the procedures (staff time, materials, capital equipment). This collected detailed information on resource use within the endoscopy units in terms of time usage, equipment and personnel, and also allowed average endoscopic practice to be calculated to ensure that standard treatment and resource use was carried out in all centres. The majority of procedures and investigation costs were also provided by the local NHS Trusts accountants, who were approached and asked to provide unit cost estimates of all individual items of resource use, investigations, interventions, inpatient stays and outpatient attendances. Radiotherapy-related treatment and procedure costs were taken from the nationally agreed NHS costs database. The acquisition costs for the metal stents and rigid tubes were taken directly from manufacturers' recommended retail prices. In this regard, for the purposes of this study, the manufacturers of the SEMS and the rigid endoprostheses kindly agreed to fix the price of these for the duration of the study in the allocated study centres. All inpatient stay costs were derived using data from the 2001 NHS Reference Costs, and to calculate costs per patient, the cost per day by speciality was multiplied by the observed length of stay in each speciality.[300] Day-case and outpatient care was costed by multiplying the frequency of visits by the unit cost estimates. Drug costs were calculated using the British National Formulary.

In this fashion, a set of average unit costs for each item of resource use was generated (unit cost table), which could be used to calculate individual cost data from the resources consumed, and a profile of resource use could then be built for each patient (Appendix 3). Total costs per patient were therefore derived by summing all inpatient, day-case, outpatient, drug, procedure and test costs.

Economic analysis

The data were split into cost of the initial treatment and associated hospital stay, the cost of all interventions from randomisation to death, the cost of all hospital stay from randomisation to death (including hospital hospice stay) and the overall total cost (which equated to the total intervention cost plus the hospital stay cost). These data could then be compared between treatment arms. Since cost data are invariably skewed, analyses were performed, including non-parametric bootstrapping and log transformations of the data. Non-parametric bootstrapping was used to generate non-parametric cost and QALY estimates. One-thousand replications of cost differences (metal group minus non-metal group) and QALY differences (metal group minus non-metal group) were produced and plotted on a four-quadrant diagram that depicted cost and QALY differences (the cost-effectiveness plane). This allowed the production of a cost-effectiveness acceptability curve, showing the probability of metal stents being cost-effective at various thresholds of cost-effectiveness. To explore the effect of changes in the price of metal stents on cost differences, sensitivity and threshold analyses were conducted. One-way sensitivity analysis involved identification

of the highest contributing variables to the total cost per patient (key cost drivers) and the effect of variation of these on total cost. The midpoint (baseline) unit cost for these drivers was varied by 25% around this baseline and the lower and upper values obtained were used to calculate new mean total costs for the two main treatment groups, which were again compared for differences between groups using non-parametric analysis.

Health state valuation methods

Patients rated health status at baseline, 3 weeks, 6 weeks and every 6 weeks thereafter using the EQ-5D instrument, to which previously published general population tariff values could then be applied.[301] In addition, a separate health state valuation study was conducted to determine the quality of life effects associated with a variety of treatment and health outcome scenarios. These were derived using information from in-depth qualitative interviews with patients, supplemented by experienced clinical input. Participants were recruited from a database of patients who had previously received curative treatment for oesophageal cancer at the NOGU. Criteria for eligibility were previous treatment for histologically proven primary ACA or SCC of the oesophagus, with associated dysphagia and greater than 6 months following potentially curative surgery with no current symptoms or signs of recurrence. Patients were invited to participate in the study by telephone, after which an information sheet and consent form were sent to those who wished to be interviewed.

Eligible patients were randomised to receive one of two health state valuation methods: the SG or the TTO method. Each patient was asked to value two main effects: treatment-related scenarios and dysphagia-specific health states. With the former, a description of the procedures was given, with information on expected number of trips to hospital required during the treatment course, number of nights to be spent in hospital, and degree of pain during and immediately following treatment. For the latter, the health state of a hypothetical patient previously treated for oesophageal cancer was described, which included different levels of dysphagia severity. These health scenarios described five health states associated with inoperable oesophageal cancer, ranging from mild to severe. Level of dysphagia, symptoms and subsequent consequences for daily activities were listed in bullet point form.

All interviews were conducted in participants' homes by an experienced healthcare interviewer. Visual aids were used to enhance patient understanding of the valuation exercise. In the case of the SG method, this consisted of a rotating disc, whereas for TTO, a movable double barchart was used. For both SG and TTO exercises, each treatment and health state had a 12-month time-frame, followed by death. Interviews consisted of three main stages.

Stage 1: Both TTO and SG

As a warm-up task, participants first described their own health status by circling one statement from each dimension of the EQ-5D instrument which best described their current state of health. Participants then read all of the five health states in turn. They were asked to envisage how they would feel living in the different states. After this, they were informed that they would be asked to rank the states from best to worst. They were instructed to make these decisions in accordance with what they would choose for themselves if faced with the options presented.

Stage 2: TTO valuation

Participants were asked to choose between two certain options: worse health for a longer period of months (duration t) followed by death, or better health for a shorter period of months (duration x) followed by death. The participant initially valued the health state they ranked best against an anchor state of good health. The specific stages were:

1. Set x equal to t to ensure that the participant understood the process, i.e. given two options: live for 12 months in good health and then die, or live for 12 months in the health state described on the card ranked best and then die.
2. Set x equal to 1 day.
3. Vary x in a 'ping-pong' fashion in steps of 1 month, until the participant was indifferent between the alternatives.
4. Using the chained approach, the interview proceeded with the participant valuing the health states against each other, i.e. health state ranked 1 ($h1$) against health state ranked 2 ($h2$), 2 against 3 ($h3$), 3 against 4 ($h4$) and 4 against 5 ($h5$).
5. Values for each state were found using equations:

$$h1 = x/t,\ h2 = h1 \times x/t,\ h3 = h2 \times x/t,\ h4 = h3 \times x/t,\ h5 = h4 \times x/t$$

Stage 2: SG valuation

Participants were asked whether they would choose to live in health state x, or take a risk and choose a

health state with probability p of living in a better health state or 1-p of immediate death. Probability p was varied until the participant was indifferent to either choice. As with TTO, the best health state was compared against the anchor state of good health from the first question. The specific stages consisted of the following:

1. Setting p equal to x to ensure that the participant understood the process, i.e. given two options: 100% probability of living for 12 months in good health and then dying, or the certain option of living in the time defined health state described on the card ranked best (*hi*) and then dying.
2. A gamble with chance p (10%) to gain the best outcome of the gamble (good health) and chance $1 - p$ (90%) of attaining the worst outcome of the gamble (immediate death).
3. Chance p was varied systematically in intervals of 10% in a 'ping-pong' fashion until the participant was indifferent between continued life in the health state ranked best and taking a gamble. Using the chained approach, health state ranked 1 was then compared with health state ranked 2, followed by 2 versus 3, 3 versus 4 and 4 versus 5. At the indifference point, values of the health states $h1$, $h2$, $h3$, $h4$ and $h5$ were calculated using the following expected utility equations:

$$h1 = p, h2 = h1 \times p, h3 = h2 \times p, h4 = h3 \times p, h5 = h4 \times p$$

4. Following the health state valuation exercise, the participant read the treatment scenario cards and ranked them from best treatment option to worst. Values for all three treatments then proceeded in an identical manner to that described above.

Stage 3: TTO and SG postinterview evaluation

After the interview, the participant was asked how easy or difficult they found the valuation exercises. Comments about the interview were recorded verbatim. The interviewer also recorded their perception of the interview quality.

Protecting against bias

Research staff and patients were blinded to the received stent treatments. However, it was not possible to maintain blindness for the patients for the non-stent treatment arm of the study as they received these interventions on a repetitive basis. Psychosocial outcomes, such as swallowing assessment or EuroQol, were blind at outcome since patients self-completed or completed with the assistance of a relative or friend who was blind to the type of palliative modality used, and in terms of the key outcome, dysphagia score, it was not felt that this lack of blindness biased participant responses, although some kind of placebo effect could not be completely ruled out.

Analysis

Data were entered on to a central Microsoft Access® database set up by a designated database manager. All data entry was checked by the clinical research fellow. Numerical EORTC quality of life questionnaire data were entered on to a separate SPSS® database by a professional data processing firm. These data were double punched. The Access® data were transferred to the SPSS statistical package for complex analysis. Analysis was intention to treat, so that patients randomised to a group remained allocated to this group even if the treatment failed and another therapy was required and this included rerandomisation. Groups were compared at single time-points using tests for independent samples as appropriate: Student's *t*-test, Fisher's exact and Mann–Whitney, for example. Changes in the two groups over time were investigated using paired t-tests and the Wilcoxon rank sum test. Differences in the way groups change over time were investigated using analysis of covariance, and the MLn package was used to fit multilevel models with occasions nested within individual patients. Variation between occasions and variation between patients were modelled as random effects, and differences between experimental groups treated as fixed effects. Standard Cox regression and Kaplan–Meier analysis were used to investigate survival effects between groups, and sensitivity analysis was undertaken to determine the extent of bias induced by differences in survival causing systematic differences in outcome. Subgroup analysis was used to compare the two types of SEMS and to compare between the non-SEMS modalities.

Chapter 3

Results

Recruitment

Actual recruitment is shown in *Figure 4* and *Table 10* in relation to target values.

Recruitment per study centre

The total recruitment per centre is represented in *Figure 5* in conjunction with the forecast value for patient entry, expected before study commencement.

Exclusions

In total, 695 patients were assessed for eligibility of study entry, 478 (69%) were excluded and 217 (31%) deemed eligible for randomisation (CONSORT flowchart: Appendix 4). Of the excluded patients, 145 were female (30.3%) and 333 male (69.7%), equating to a male to female ratio of approximately 2:1. The mean age of this group was 68.3 ± 12.5 years, significantly lower

TABLE 10 *Overall centre recruitment versus total target recruitment*

	Bristol	Carlisle	Newcastle	Portsmouth	Southampton	Winchester	Edinburgh	Total	Target
1999									
January	0	0	0	0	0	0	0	0	19
February	0	0	8	1	0	0	0	9	38
March	0	0	1	1	1	0	0	12	57
April	4	2	5	1	1	0	0	25	76
May	2	1	6	0	1	1	0	36	95
June	2	1	4	4	0	0	0	47	114
July	0	0	3	1	1	0	0	52	133
August	3	2	2	1	2	0	0	62	152
September	1	2	2	6	1	4	0	78	171
October	1	0	2	2	1	0	0	84	190
November	1	0	3	2	1	2	0	93	209
December	1	1	3	0	2	1	0	101	228
2000									
January	0	0	1	0	0	0	0	102	247
February	2	0	2	2	1	0	0	109	266
March	1	0	5	2	2	1	0	120	285
April	0	0	4	3	1	2	1	131	300
May	1	0	5	2	3	0	1	143	300
June	0	1	3	1	1	0	2	151	300
July	1	2	3	2	2	0	4	165	500
August	0	2	4	2	0	1	2	176	300
September	0	0	4	0	1	0	1	182	300
October	1	1	2	2	0	0	2	190	300
November	0	0	2	3	0	0	0	195	300
December	0	0	1	0	0	0	2	198	300
2001									
January	0	0	1	2	0	0	0	201	300
February	0	0	0	1	0	1	1	204	300
March	0	0	7	2	0	0	1	214	300
April	0	0	3	0	0	0	0	217	300
Total	21	15	86	43	22	13	17	217	300
Predicted	67	45	90	112	135	101	79	629	

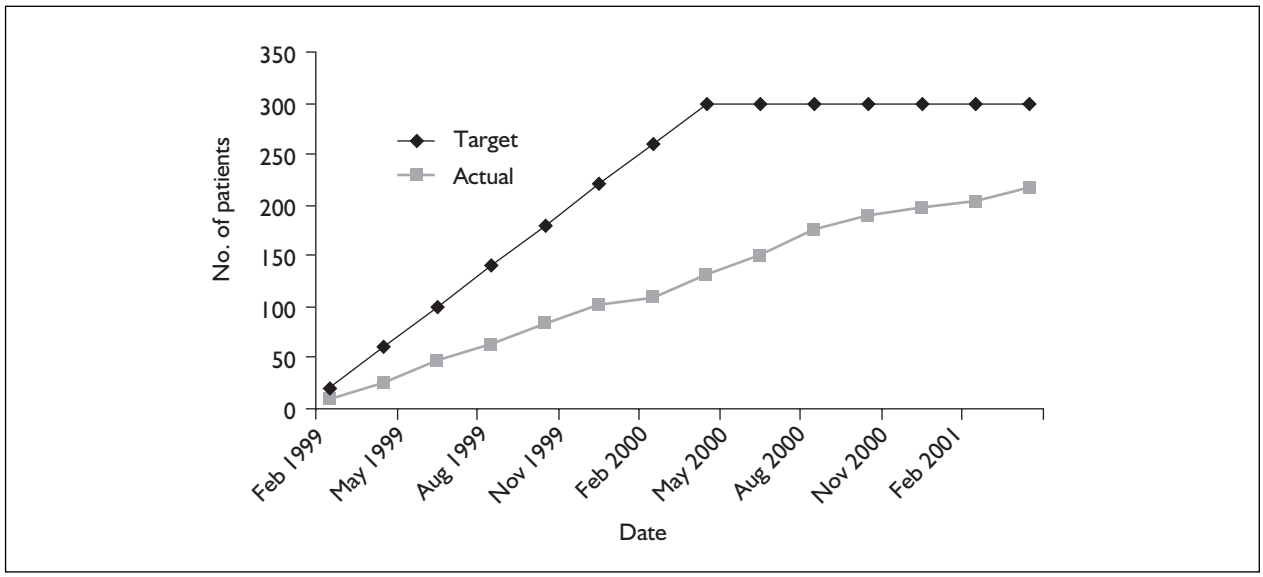

FIGURE 4 *Target total recruitment versus actual accrual*

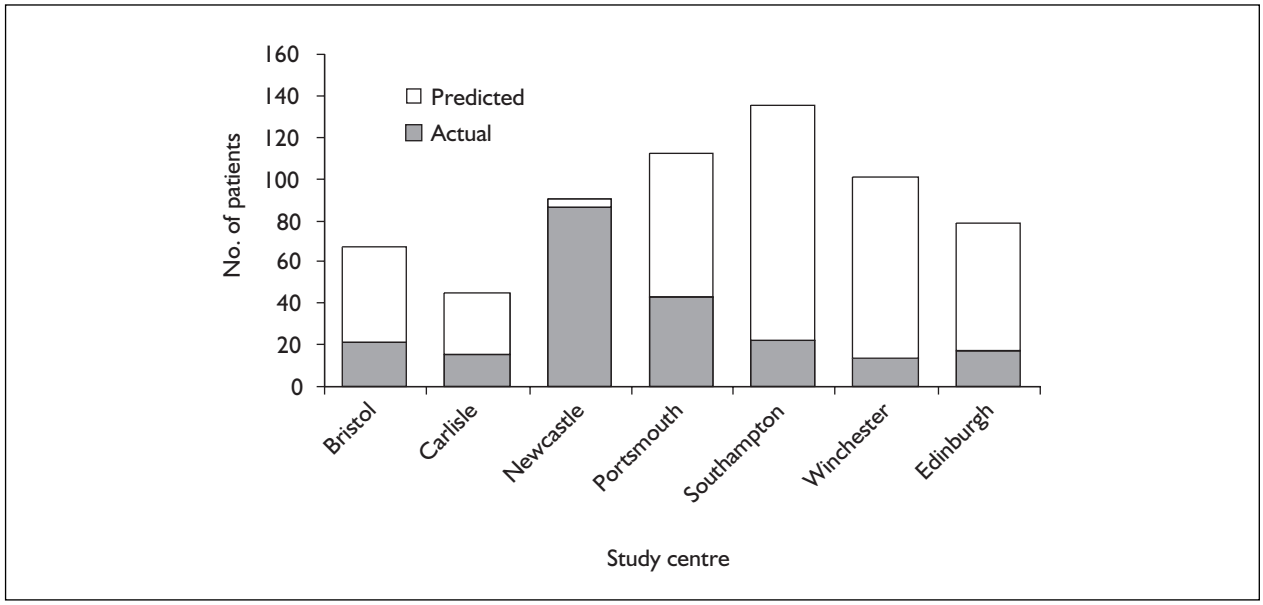

FIGURE 5 *Predicted recruitment versus actual recruitment*

than the patients satisfying the entry criteria ($p < 0.0001$). Since the 95% confidence interval (CI) for the difference in mean age between these groups was 4.6 to 8.4 years this equates to the excluded patients being on average 6.5 years younger than included patients. This difference is likely to arise from patients with operable or potentially operable lesions who then underwent surgery or neoadjuvant treatment, as this group had a mean age of 65.1 ± 11.0 years versus 86.3 ± 13.2 years for the remaining excluded but inoperable patients ($p < 0.0001$, 95% CI 19.0 to 23.4 years).

Failure to meet entry criteria accounted for 91% of exclusions (*Table 11*), two-thirds of whom ($n = 293$) were suitable for potentially curative treatment. Only 4% of assessed patients ($n = 27$) refused study entry, the majority of whom had predetermined preferences for treatment (*Table 12*). A further 14 patients were excluded for other reasons: one patient left the country after

TABLE 11 *Exclusions*

Exclusions	No. of patients
Did not meet entry criteria	437
Refused	27
Other	14
Total	**478**

TABLE 12 *Refusal of study entry*

Refused	No. of patients
Treatment preference	9
Did not want to be part of a trial	7
Refused all treatment	7
Logistical refusal, e.g. distance to treatment centre	4
Total	**27**

diagnosis and 13 patients had no reason documented for study exclusion.

Randomisation

In total, 217 subjects were randomised. The proportion of treatment group randomisations per centre is shown in *Table 13*. The computer-generated block randomisation ensured an equivocal spread of randomised treatments within the study centres.

Assessments

In total, 897 assessments (mode 4, range 1–17) were performed. Six subjects did not undergo baseline assessment despite assessment at a later stage; four of these patients underwent a week 1 assessment. However, 186 patients (90%) of patients had a week 1 assessment. Seventy-two subjects were not able to have an assessment at week 6; one had an assessment at week 7 and two others had an assessment at week 4, and scores at these time-points were used as proxies for the week 6 scores for these three subjects. Outcome at 6 weeks was therefore based on an analysis of 138 subjects, equating to an attrition rate of 33%.

TABLE 14 *Table of withdrawals*

Reason for withdrawal	No. of patients
Voluntary	8
Immediate	2
Inappropriate randomisation	6
Left the country	1
Total	**17**

Withdrawals

In total, 17 patients (8%) withdrew from the study (*Table 14*); eight withdrew voluntarily, all of whom had been in the study for at least 1 month (median 113 days, range 35–369 days); these patients no longer wished to answer study questions as they had become terminally ill; two further patients withdrew following randomisation having changed their mind about the study; and one patient left the country during the study period and was lost to follow-up. Six patients should not have been randomised as five did not satisfy the study entry criteria and one was mistakenly randomised twice.

Demographics

Sex

Sixty-four patients were female (29.8%) and 151 male (70.2%), equating to a male to female ratio of 2:1. This ratio was preserved across all four groups (*Table 15*). There were no differences between the groups in the gender distribution ($\chi^2 = 2.809$, 3 df, $p = 0.422$).

TABLE 13 *Randomisation table*

Centre	Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS	Total
Bristol	5	5	5	6	21
Carlisle	3	4	4	4	15
Edinburgh	4	5	4	4	17
Newcastle	21	23	21	21	86
Portsmouth	11	11	11	10	43
Southampton	5	5	6	6	22
Winchester	3	4	3	3	13
Total	**52**	**57**	**54**	**54**	**217**

TABLE 15 *Gender distribution between subgroups*

Treatment group	Female	Male	Total
Non-stent	11	39	50
Rigid tube	17	40	57
18-mm SEMS	16	38	54
24-mm SEMS	20	34	54
Total	64	151	215

Age

The mean age at entry to the study was 74.8 ± 9.0 years. The plot in *Figure 6* appears to show a difference between the groups. This approached significance on analysis (*Table 16*). The difference between groups was significant at the 10% level ($F = 2.38$, $p = 0.071$), with the SEMS groups appearing to be younger; as such, a comparison of SEMS versus non-SEMS patients was performed (*Figure 7* and *Table 17*). There was a statistically significant difference ($p = 0.011$). The 95% CI for the difference in mean age between the groups was 0.7 to 5.6 years, that is, SEMS patients were on average 3 years younger than conventionally treated patients in the study.

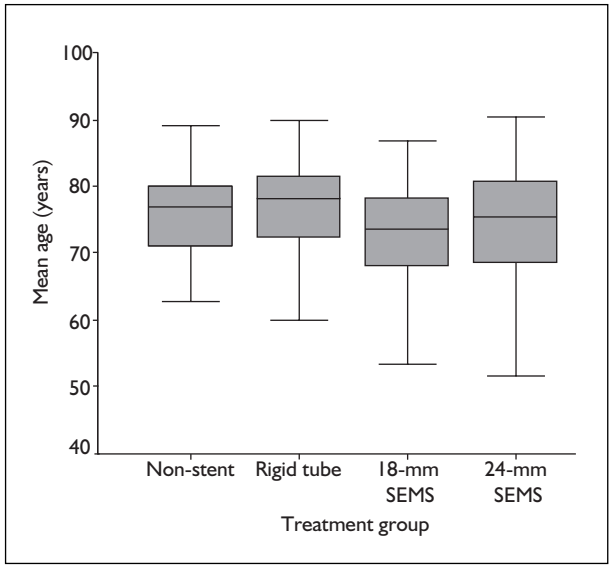

FIGURE 6 *Age by treatment group*

TABLE 16 *Age distribution between subgroups*

Treatment group	Mean age ± SD (years)
Non-stent	75.8 ± 9.0
Rigid tube	76.9 ± 7.3
18-mm SEMS	72.8 ± 7.7
24-mm SEMS	73.5 ± 11.3
Total	**74.8 ± 9.0**

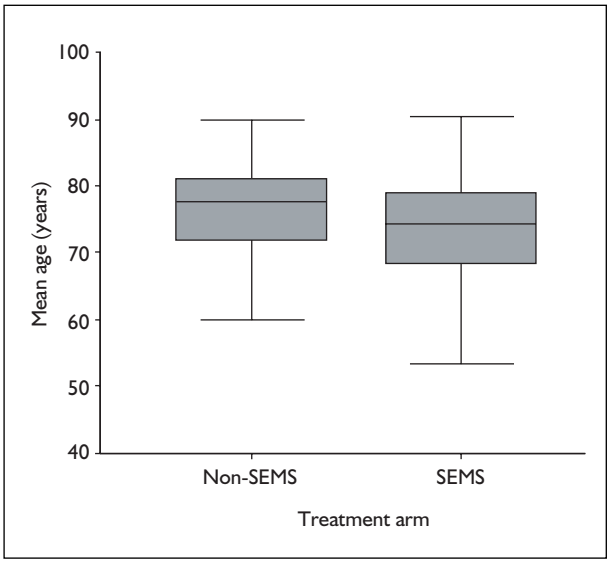

FIGURE 7 *Age by treatment arm*

Histology

In total, 122 patients (57.5%) had ACA of the oesophagus, 75 (35.4%) had SCC and 15 were unclassified (7.1%) owing to poor histological differentiation. This reflects an average oesophageal cancer population in the UK.[2,34]

TABLE 17 *Comparison of mean age between treatment arms*

Treatment group	Mean age ± SD (years)
Non-SEMS	76.4 ± 8.1
SEMS	73.2 ± 9.6

TABLE 18 *Distribution of histological subtypes between subgroups*

Treatment group	ACA	SCC	Total
Non-stent	31	16	47
Rigid tube	30	22	52
18-mm SEMS	29	22	51
24-mm SEMS	32	15	47
Total	122	75	197

TABLE 19 *Distribution of histological subtypes between treatment arms*

Treatment group	ACA	SCC	Total
Non-SEMS	61	38	99
SEMS	61	37	98
Total	122	75	197

This ratio was preserved across all four groups (χ^2 = 2.03, 3 df, p = 0.566) (*Table 18*). Similarly, there was no difference between those patients who received SEMS and those who did not (χ^2 = 0.008, 1 df, p = 0.928) (*Table 19*).

Tumour length

Mean tumour length did not differ significantly between groups or treatment arms. The mean tumour length was similar for all four groups (ANOVA Σ^2 = 19.6, 3 df, p = 0.649) (*Table 20*). There was no difference between tumour length in subjects randomised to SEMS versus non-SEMS therapies (p = 0.996) (*Table 21*).

TABLE 20 *Mean tumour length by treatment subgroup*

Treatment group	Mean tumour length SD (cm)
Non-stent	6.57 ± 3.06
Rigid tube	7.02 ± 2.98
18-mm SEMS	6.44 ± 2.45
24-mm SEMS	7.21 ± 4.91
Total	6.81 ± 3.44

TABLE 21 *Mean tumour length by treatment arm*

Treatment group	Mean tumour length SD (cm)
Non-SEMS	6.81 ± 3.01
SEMS	6.81 ± 3.84

Disease staging

Full TNM (tumour, node, metastases) staging was available for 141 (66%) of the patients randomised to the study. Ninety-eight per cent had tumour invasion through the oesophageal adventitia, 125 (88%) with nodal spread and 14 (10%) without. Only three (2%) had confined, node-negative disease; one refused surgery despite staging defined operable disease and the other two patients were elderly (88 and 89 years) and unfit for surgery, but with significant dysphagia. There were no differences between groups (Kruskal–Wallis χ^2 = 2.13, 3 df, p = 0.552) or treatment arms (p = 0.409) (*Table 22*). Insufficient data were present in 71 patients.

Inoperability

Further to staging investigations the primary reason for inoperability was documented (*Table 23*). However, in 52 cases a secondary reason was cited. There were six cases of missing data and two patients refused surgery despite being suitable, operable candidates. Ninety-seven patients (46%) were classified as unfit for surgical intervention, with the remaining 54% split equally between 53 patients with locally unresectable disease and 54 with distant metastatic spread. In 52 cases (25%) more than one reason for inoperability was cited: 39 (75%) of these cases were unfit for surgery as well as having locally advanced disease or metastatic spread and 11 (25%) had both advanced local and distant disease.

TABLE 22 *Stage of disease by treatment subgroup*

			Treatment group				
			Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS	Total
Disease stage	Missing data	Count (% within randomised to)	15 (30.6%)	15 (26.8%)	17 (32.1%)	24 (44.4%)	71 (33.5%)
	0	Count (% within randomised to)				1 (1.9%)	1 (0.5%)
	1	Count (% within randomised to)		1 (1.8%)			1 (0.5%)
	2a	Count (% within randomised to)	5 (10.2%)	3 (5.4%)	3 (5.7%)	3 (5.6%)	14 (6.6%)
	2b	Count (% within randomised to)	1 (2.0%)				1 (0.5%)
	3	Count (% within randomised to)	16 (32.7%)	20 (35.7%)	15 (28.3%)	14 (25.9%)	65 (30.7%)
	4	Count (% within randomised to)	12 (24.5%)	17 (30.4%)	18 (34.0%)	12 (22.2%)	59 (27.8%)
Total		Count (% within randomised to)	49 (100.0%)	56 (100.0%)	53 (100.0%)	54 (100.0%)	212 (100.0%)

TABLE 23 *Reason for inoperability*

Primary reason for inoperability	Secondary reason for inoperability				
	Single reason	Distant spread	Unfit	Locally unresectable	Total
Distant spread	33	–	17	4	54
Unfit	94	1	–	2	97
Locally unresectable	25	9	19	–	53

Distant spread

There were no differences in the distribution of distant spread as a cause of inoperability between the treatment groups ($\chi^2 = 0.678$, 3 df, $p = 0.88$) (*Table 24*), nor was there a difference in the distribution of distant spread as a cause of inoperability between subjects receiving SEMS and those who did not ($\chi^2 = 0.258$, 1 df, $p = 0.61$) (*Table 25*).

Locally unresectable disease

There were no differences in the distribution of locally advanced disease as a cause of inoperability between the treatment groups ($\chi^2 = 1.597$, 3 df, $p = 0.660$) (*Table 26*). Similarly, there was no difference in the distribution of locally advanced disease as a cause of inoperability between subjects receiving SEMS and those who did not ($\chi^2 = 0.297$, 1 df, $p = 0.586$) (*Table 27*).

Unfit

There were no differences in the distribution of patients who were unfit for surgical intervention between the treatment groups ($\chi^2 = 5.074$, 3 df, $p = 0.166$) (*Table 28*). However, there was a statistically significant difference in the distribution of patients who were unfit for surgical intervention between subjects receiving SEMS and those who did not ($\chi^2 = 4.10$, 1 df, $p = 0.048$) (*Table 29*).

TABLE 24 *Distant spread by treatment subgroup*

Treatment group	No distant spread	Distant spread	Total
Non-stent	36	13	49
Rigid tube	39	17	56
18-mm SEMS	35	18	53
24-mm SEMS	38	16	54
Total	148	64	212

TABLE 25 *Distant spread by treatment arm*

Treatment group	No distant spread	Distant spread	Total
Non-SEMS	75	30	105
SEMS	73	34	107
Total	148	64	212

TABLE 26 *Locally advanced disease by treatment subgroup*

Treatment group	Not locally advanced	Locally advanced	Total
Non-stent	37	12	49
Rigid tube	37	19	56
18-mm SEMS	40	13	53
24-mm SEMS	39	15	54
Total	153	59	212

TABLE 27 *Locally advanced disease by treatment arm*

Treatment group	Not locally advanced	Locally advanced	Total
Non-SEMS	74	31	105
SEMS	79	28	107
Total	153	59	212

TABLE 28 *Unfit for surgery by treatment subgroup*

Treatment group	Not unfit	Unfit	Total
Non-stent	14	35	49
Rigid tube	18	38	56
18-mm SEMS	21	32	53
24-mm SEMS	26	28	54
Total	79	133	212

TABLE 29 *Unfit for surgery by treatment arm*

Treatment group	Not unfit	Unfit	Total
Non-SEMS	32	73	105
SEMS	47	60	107
Total	79	133	212

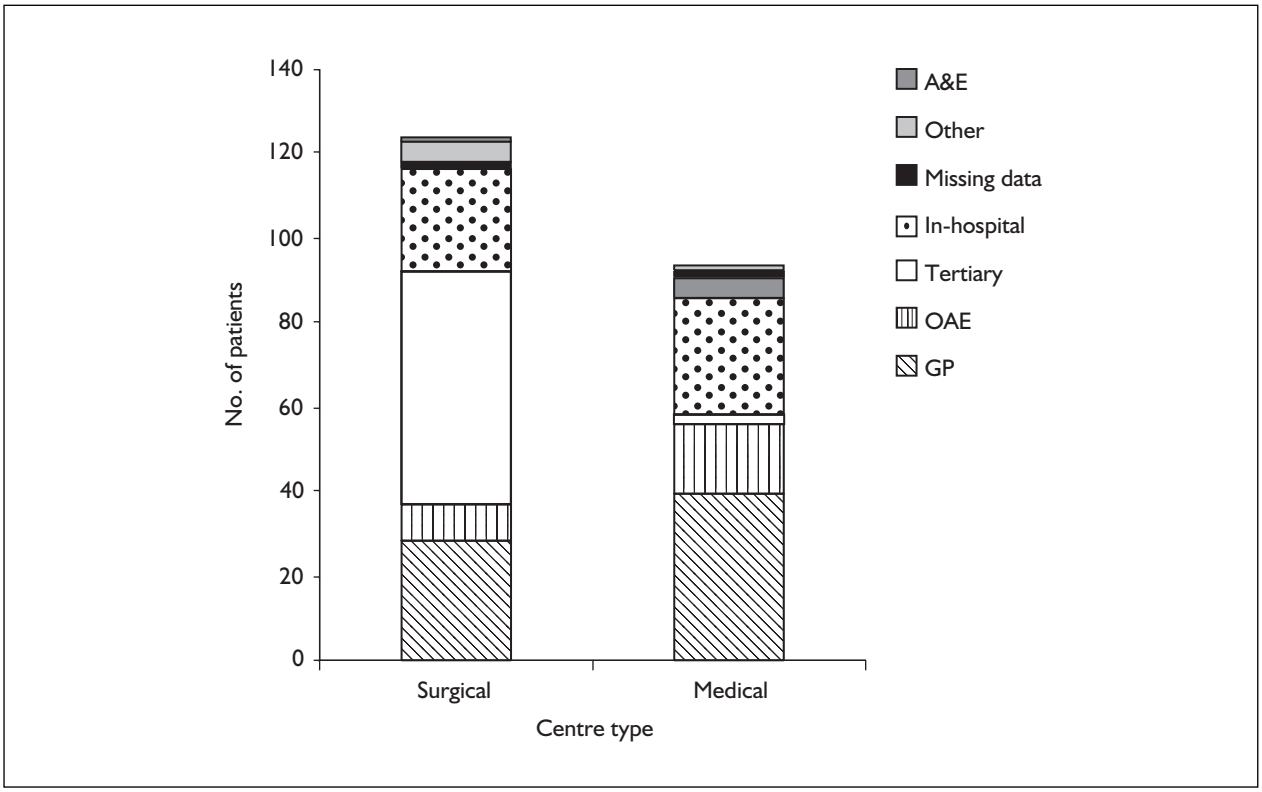

FIGURE 8 *Number of referrals by centre type. A&E, accident & emergency; OAE, open-access endoscopy.*

Referral method

There was a 60:40 split between referrals to predominantly surgical centres (Bristol, Carlisle and Newcastle upon Tyne: $n = 122$) and those to predominantly medical centres (Edinburgh, Portsmouth, Southampton and Winchester: $n = 93$) (*Figure 8*). In total, 93 patients (43%) were referred by their GP for evaluation or treatment, with 26 (28%) of these directly referred via open-access endoscopy services. Open-access referrals were more common in medical study centres and tertiary referrals more common in surgical centres ($\chi^2 = 35.3$, $p < 0.001$) (*Table 30*).

Delay, length of stay and admissions

Delay to treatment

The time from randomisation to treatment is displayed graphically in *Figure 9* for all patients. Despite the majority of patients receiving treatment within the first week following randomisation, this log-plot of time to treatment from time of randomisation has a long tail. This is explored further in *Table 31*. There was a significant difference in the mean delay between randomisation and treatment between the groups (Kruskal–Wallis $\chi^2 = 9.42$, 3 df, $p = 0.024$), but

TABLE 30 *Types of referral*

Type of referral	Study centre		Total no. of patients
	Surgical	Medical	
GP	28	39	67
Open-access endoscopy	9	17	26
Tertiary	55	2	57
In-hospital	24	28	52
Missing data	1	6	7
Other unspecified	5	0	5
Accident & emergency	0	1	1
Total	122	93	215

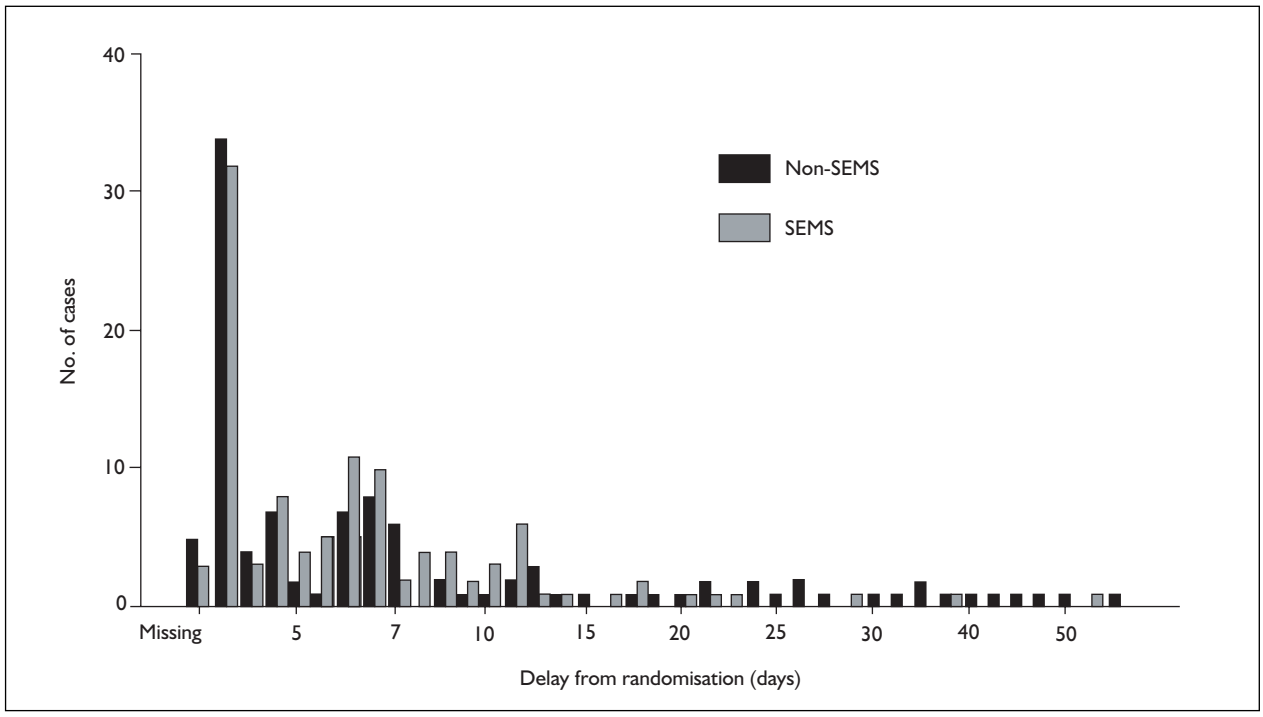

FIGURE 9 *Histogram of delay (days) from randomisation to treatment*

TABLE 31 *Mean delay from randomisation to treatment by treatment subgroup*

Treatment group	Mean delay ± SD (days)
Conventional care	13.4 ± 13.9
Rigid tube	11.6 ± 48.7
18-mm SEMS	8.5 ± 21.7
24-mm SEMS	5.4 ± 5.5

TABLE 32 *Comparison of mean delay between radiotherapy and non-radiotherapy non-stent patient groups*

Conventional care	*n*	Mean delay ± SD (days)	*t*-test *p*-value
Non-radiotherapy	23	9.09 ± 11.1	0.009
Radiotherapy	26	19.5 ± 15.1	

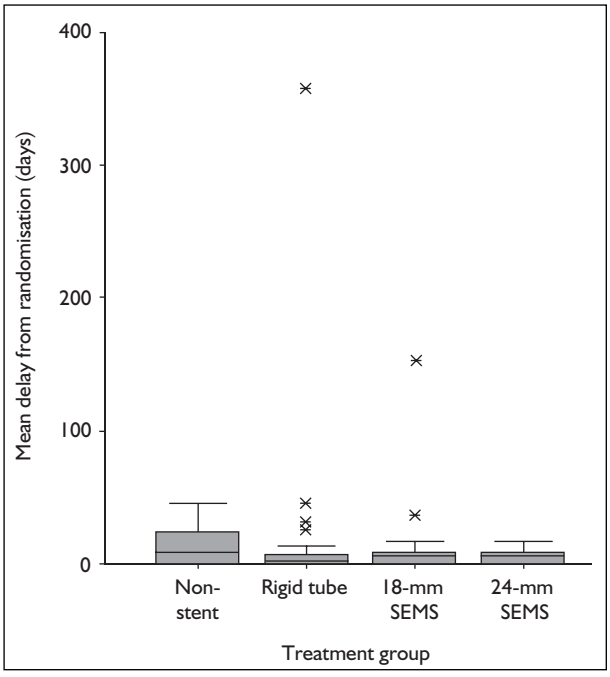

FIGURE 10 *Delay versus treatment subgroup*

initial analysis did not confirm that SEMS patients suffered less delay, despite this apparent observation ($p = 0.388$). However, there was considerable skewing of mean data owing to the long tail and outlying values, as demonstrated in a boxplot of mean delay to treatment (*Figure 10*). The outlying values represent patients who did not require treatment for dysphagia at the time of randomisation, but were entered into the study and randomised to await treatment when it became necessary. When these data were replotted without the outliers (*Figure 11*), it became clear that the apparent difference between the groups was due to a significant delay for those

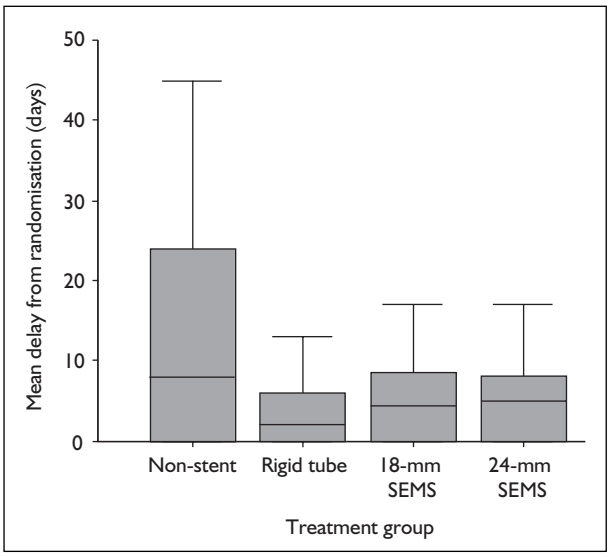

FIGURE 11 *Delay (days) versus treatment subgroup minus outliers*

randomised to a non-stent treatment (Mann–Whitney $U = 2771.0$, $p = 0.003$). Even within this subgroup that there was a further difference between patients who received radiotherapy and those treated by other means (*Table 32*).

Length of stay and number of admissions

Initial

The length of inpatient stay in days during the initial admission for palliative treatment (*Figure 12*) was highly skewed by a small number of long-stay patients. Removal of outlying values on a plot of the data appeared to demonstrate underlying differences between the groups, and non-parametric analysis of all data confirmed a highly significant difference between the treatment groups ($\chi^2 = 14.2$, 3 df, $p = 0.002$). However, there was no difference between the initial stays of SEMS and non-SEMS patients (Mann–Whitney $U = 4734.5$, $p = 0.18$). The difference between the groups stemmed from the subgroup of patients receiving non-stent treatments. In this subgroup the length of initial stay was considerably shorter than in the three stent treatment subgroups (Mann–Whitney $U = 2525.5$, $p < 0.001$). The three stent treatment subgroups had comparable initial admission stays.

Total stay

The total length of inpatient stay is shown in *Figure 13* by treatment group. Again, the data were skewed by outlying data, but less so than with the initial stay data. Analysis confirmed the findings of the simple boxplot: median total stay was longer for the non-stent and 18-mm SEMS patients than for other treatments. This significant difference between groups was confirmed by analysis (Kruskal–Wallis $\chi^2 = 9.85$, 3 df, $p = 0.018$), but when SEMS were compared with non-SEMS therapies this difference was cancelled out by the combination of treatments ($p = 0.32$).

Admissions

The total numbers of admissions for the patients in the treatment groups were compared (*Figure 14*). Those who received non-stent treatments had more admissions than the other treatment groups (*Table 33*). This difference was highly significant (Mann–Whitney $U = 1834.5$,

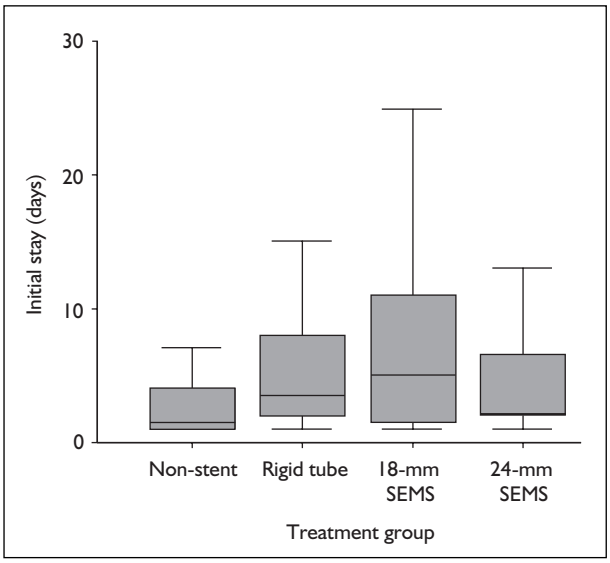

FIGURE 12 *Length of initial hospital inpatient stay by treatment subgroup*

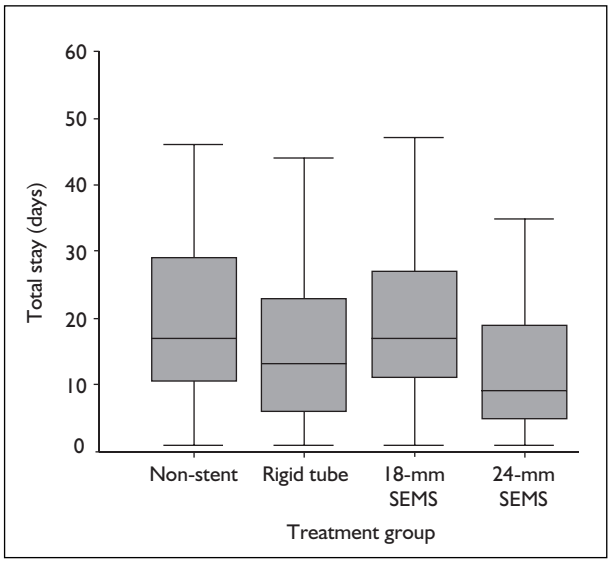

FIGURE 13 *Length of total hospital inpatient stay by treatment subgroup*

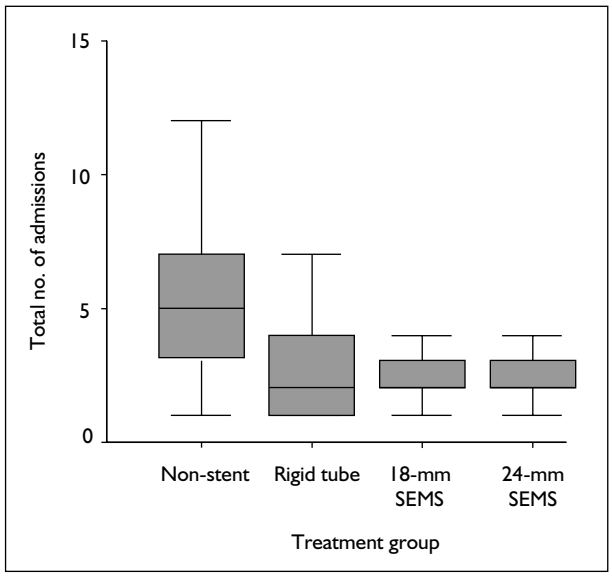

FIGURE 14 *Number of admissions by treatment subgroup*

TABLE 33 *Median number of admissions by treatment subgroup*

Treatment group	Median no. of total admissions	Range
Non-stent	5	1–16
Rigid tube	2	1–9
18-mm SEMS	2	1–6
24-mm SEMS	2	1–23

$p < 0.001$), with the remaining three stent groups not significantly different at the 5% level ($\chi^2 = 5.3$, $p = 0.069$).

Correcting for length of life

Total hospital stay and the number of hospital admissions that a patient requires are affected in part by their length of life as, in general, the longer patients survive the more likely they are to require inpatient activity. As such, the data required correction for this potential effect.

Hospital stay by survival

A simple scatterplot of length of total hospital stay against length of life suggested a relationship (*Figure 15*). Analysis confirmed this correlation as being highly significant (*Table 34*). However, comparing the treatment groups after correction for length of life demonstrated no difference in the total length of hospital stay per week of life between groups ($\chi^2 = 5.61$, 3 df, $p = 0.131$), and

TABLE 34 *Correlation between total hospital stay and survival*

	Correlation	Time to death (weeks)	*p*-Value
Total stay and Survival	Pearson	0.350	0.000

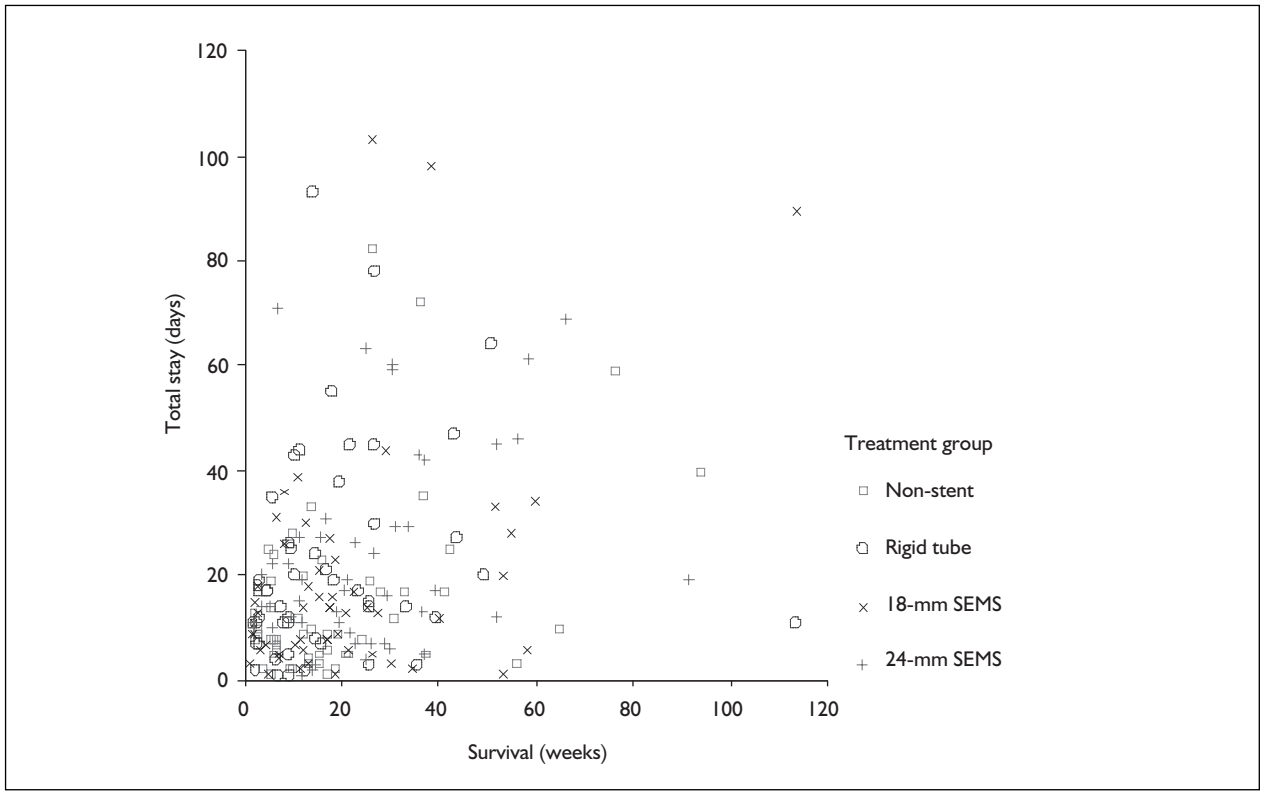

FIGURE 15 *Total stay versus survival*

this is also the case when comparing the SEMS patients with non-SEMS patients (Mann–Whitney $U = 5004.5$, $p = 0.56$). This can be observed on a boxplot (*Figure 16*).

Number of admissions by survival

The total number of admissions was similarly related to length of life, and this relationship is demonstrated on a further scatterplot (*Figure 17*). This correlation is again highly significant (*Table 35*). However, there was no difference between the treatment groups in the total number of hospital admissions by length of life ($\chi^2 = 4.83$, 3 df, $p = 0.186$), or between SEMS and non-SEMS treatments (Mann–Whitney $U = 4900.5$, $p = 0.404$) (*Figure 18*). Previous analysis of the non-stent-treated patients demonstrated a significantly greater number of admissions to the other three groups, and although correction for length of life demonstrated no difference in total length of stay in this subgroup (Mann–Whitney $U = 3693.0$, $p = 0.84$), the total number of admissions remained significantly higher for patients (Mann–Whitney $U = 2999.0$, $p = 0.032$), despite a reduction in the size and significance of this difference ($p < 0.001$ to $p = 0.032$).

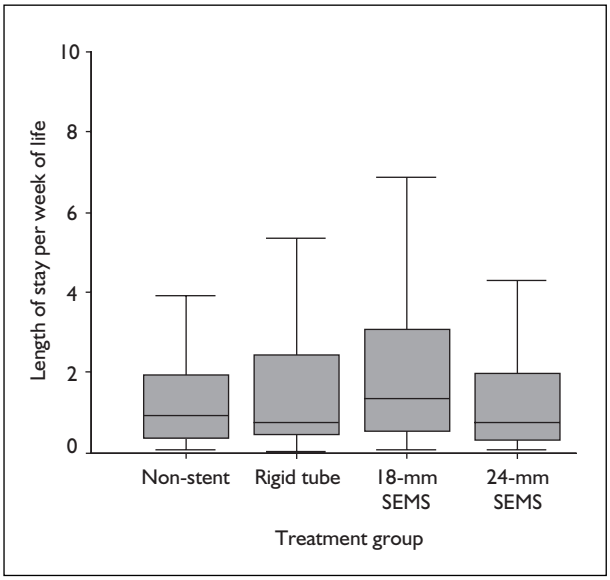

FIGURE 16 *Total length of stay per week of life*

TABLE 35 *Correlation between total number of admissions and survival*

	Correlation	Time to death (weeks)	*p*-Value
Total no. of admissions and survival	Pearson	0.485	0.000

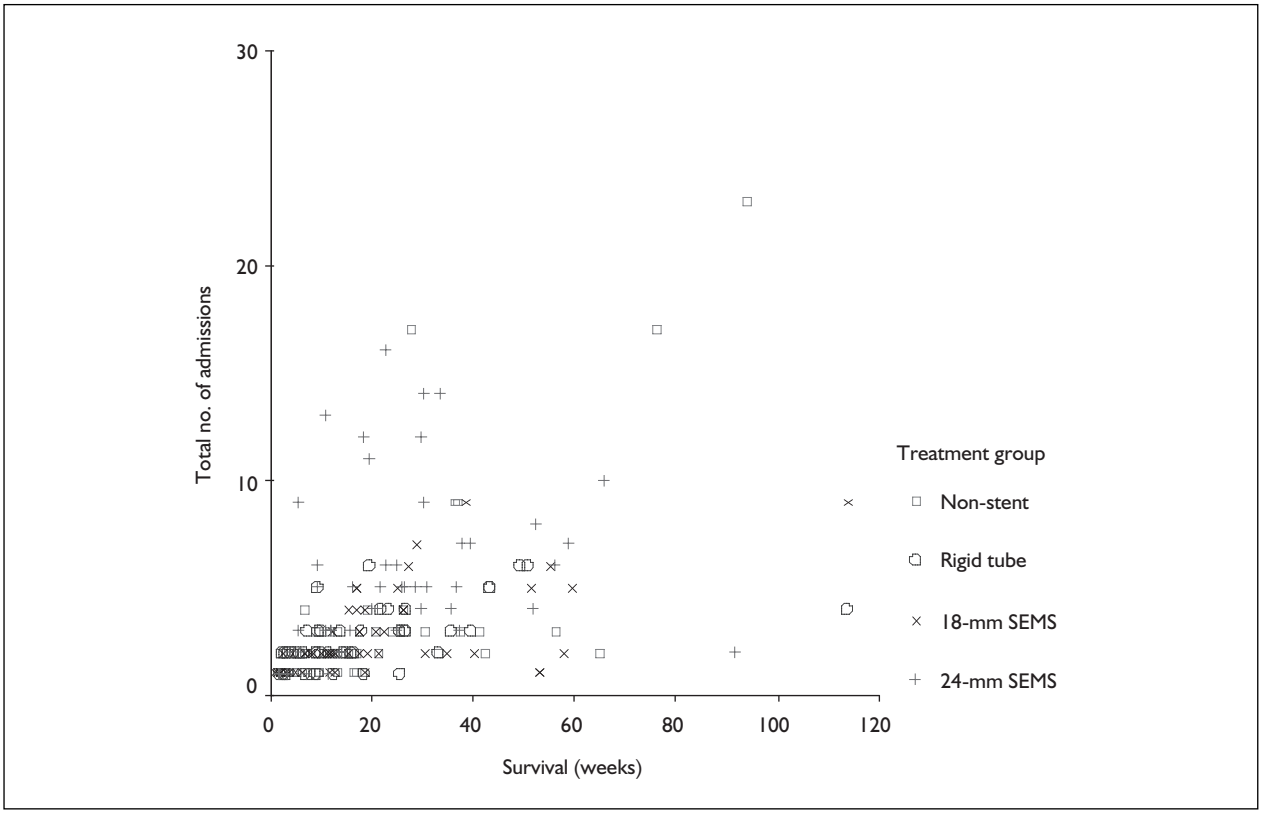

FIGURE 17 *Total number of admissions versus survival*

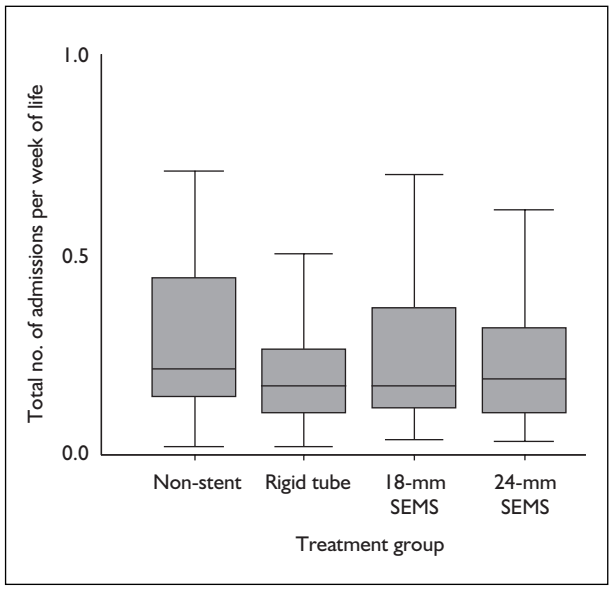

FIGURE 18 *Number of admissions per week of life*

Dysphagia

Over two-thirds of patients had an improvement in swallowing ability from the baseline assessment to the 6-week assessment following treatment (n = 90) (*Table 36*). In some subjects there were dramatic improvements in dysphagia. However, 17 subjects had a poorer dysphagia score at 6 weeks than at baseline and 31 subjects had the same scores at 6 weeks and baseline, although seven subjects who could eat normally at baseline could not be expected to improve (ceiling effect). There was a suggestion of baseline imbalance in mean dysphagia score, with a difference that approached significance between the two main treatment arms (p = 0.09). This was also present between the groups at 6 weeks (ANOVA Σ^2 = 6.87, 3 df, F = 2.13, p=0.099), but not between those treated by SEMS and those not treated by SEMS (*Tables 37* and *38*). This was the main result for the primary outcome measure; therefore, the effect of treatment with a metal stent (relative to other treatments) was a change in dysphagia score of –0.18 (95% CI –0.54 to +0.17), where the negative sign indicates an improvement in swallowing ability. The difference noted between the groups was due to significantly worse swallowing at 6 weeks in patients treated by rigid intubation (*Table 39*). Median scores were essentially similar for all groups at baseline, with 18-mm SEMS having a one-point advantage over the others at 6 weeks (*Table 40*).

TABLE 37 *Mean dysphagia scores by treatment subgroup*

Treatment group	Baseline mean dysphagia score ± SD	Week 6 mean dysphagia score ± SD
Non-stent	1.75 ± 0.84	0.86 ± 0.96
Rigid tube	1.94 ± 0.98	1.42 ± 1.00
18-mm SEMS	2.09 ± 0.96	0.91 ± 1.17
24-mm SEMS	2.15 ± 0.99	1.00 ± 1.02

TABLE 38 *Mean dysphagia scores at 6 weeks by treatment arm*

Treatment group	Week 6 mean dysphagia score ± SD	*t*-Test *p*-value
Non-SEMS	1.14 ± 1.01	0.304
SEMS	0.95 ± 1.09	

TABLE 39 *Mean dysphagia scores at 6 weeks between rigid tube and non-rigid tube groups*

Treatment group	Week 6 mean dysphagia score ± SD	*t*-Test *p*-value
Non-rigid tube	0.92 ± 1.04	0.014
Rigid tube	1.42 ± 1.00	

TABLE 36 *Dysphagia grade at baseline by dysphagia grade at 6 weeks*

Dysphagia grade at 6 weeks	Dysphagia grade at baseline					Total
	Normal	Difficulty solids	Difficulty semi-solids	Difficulty liquids	Absolute	
Normal	3	15	22	12	2	54
Difficulty solids	1	12	17	8	1	39
Difficulty semi-solids	3	6	12	8	2	31
Difficulty liquids	0	2	6	3	1	12
Absolute	0	0	0	1	1	2
Total	7	35	57	32	7	138

TABLE 40 *Median dysphagia scores at 6 weeks by treatment subgroup*

Treatment group	Baseline median dysphagia score (range)	Week 6 median dysphagia score (range)
Non-stent	2 (0–4)	1 (0–3)
Rigid tube	2 (0–4)	1 (0–4)
18-mm SEMS	2 (0–4)	0 (0–3)
24-mm SEMS	2 (0–4)	1 (0–4)

TABLE 41 *Dysphagia grade by time*

Dysphagia pairing	Mean dysphagia grade ± SD	*t*-Test *p*-value
Baseline	1.31 ± 0.90	0.000
Week 1	1.98 ± 0.91	
Week 1	1.31 ± 0.90	0.018
Week 6	1.05 ± 1.06	

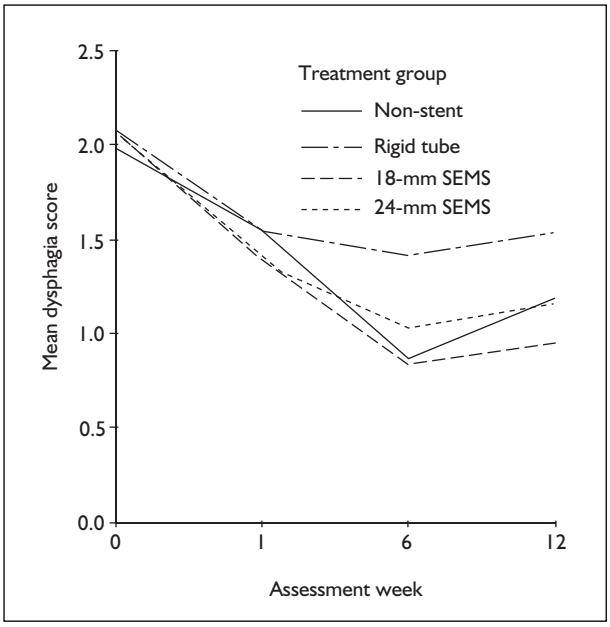

FIGURE 19 *Dysphagia grade by time and treatment subgroup*

Dysphagia grade versus time

It appears from the plot of mean dysphagia scores (*Figure 19*) that there was a significant improvement in dysphagia from baseline to the week 1 assessment, and from week 1 to week 6. This is confirmed by statistical analysis (*Table 41*).

Predictive value of baseline dysphagia grade

The correlation between dysphagia scores at baseline and dysphagia scores at 6 weeks was low, as demonstrated by analysis of covariance (*Table 42*). It could be that those who survived to the 6-week assessment differed at baseline from those who did not survive, a variant of a response bias. However, there was no evidence of large differences at baseline between those who made it to 6 weeks and those who did not (*Table 43*).

Nutrition

Various nutritional parameters were examined. There were no significant differences between any groups in the analysis. The changes in BMI and grip strength were typical of these results.

Body mass index

There was a general decline in mean BMI with all treatments, but there were no differences between treatment groups or subgroups (*Figure 20*). The difference between groups was not significantly different at baseline (ANOVA $\Sigma^2 = 61.0$, 3 df,

TABLE 43 *Differences in baseline dysphagia grade for those surviving to 6 weeks*

6-week assessment?	*n*	Baseline mean dysphagia grade ± SD	*t*-Test *p*-value
No	67	2.18 ± 0.92	0.152
Yes	138	1.98 ± 0.95	

TABLE 42 *Analysis of covariance for dysphagia grade*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	10.1693508	4	2.54233769	2.41	0.0526
Baseline dysphagia	3.29872878	1	3.29872878	3.12	0.0795
Random	6.86589095		2.28863032	2.17	0.0949
Residual	140.475577	133	1.05620734		
Total	150.644928	137	1.09959801		

No. of observations = 138, $R^2 = 0.0675$, adjusted $R^2 = 0.0395$, root mean square error (MSE) = 1.02772.
SS, sum of square; ms, mean square.

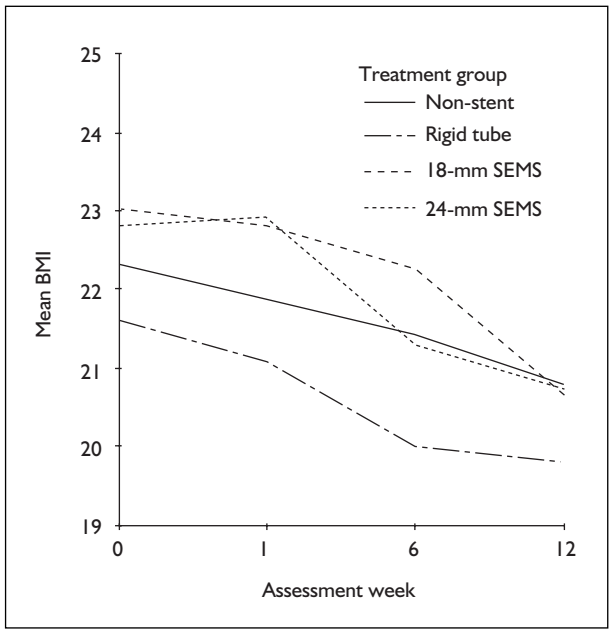

FIGURE 20 *Mean BMI by time and treatment subgroup*

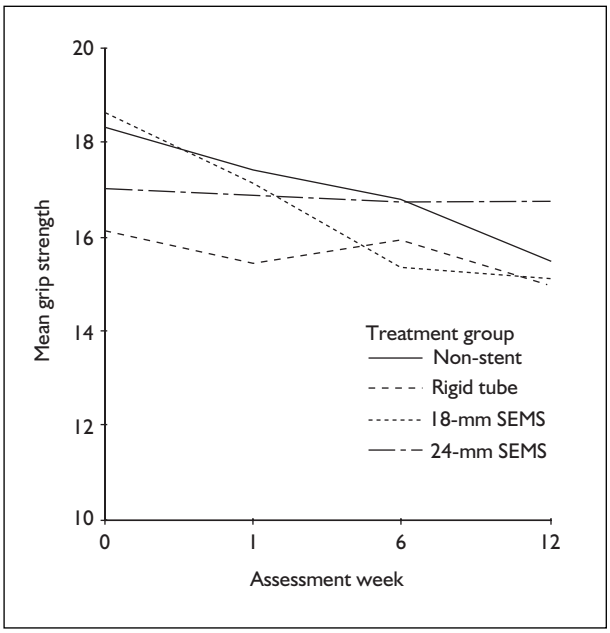

FIGURE 21 *Mean grip strength by time and treatment subgroup*

TABLE 44 *Mean BMI at baseline and 6 weeks for treatment subgroups*

Treatment group	Baseline mean BMI ± SD	Week 6 mean BMI ± SD
Non-stent	22.5 ± 3.47	19.7 ± 7.17
Rigid tube	21.5 ± 3.61	18.2 ± 6.75
18-mm SEMS	23.5 ± 5.62	19.25 ± 9.44
24-mm SEMS	22.7 ± 4.00	18.6 ± 8.26

TABLE 45 *Mean grip strength at baseline and 6 weeks for treatment subgroups*

Treatment group	Mean baseline grip strength ± SD	Mean week 6 grip strength ± SD
Non-stent	18.3 ± 8.45	17.09 ± 7.68
Rigid tube	16.12 ± 7.44	15.94 ± 6.26
18-mm SEMS	18.64 ± 8.03	15.35 ± 6.2
24-mm SEMS	16.98 ± 9.28	16.25 ± 8.51

$F = 1.159$, $p = 0.329$) or at 6 weeks (ANOVA $\Sigma^2 = 43.7$, 3 df, $F = 0.232$, $p = 0.874$). Similarly, there were no significant differences at baseline ($p = 0.155$) or at 6 weeks ($p = 0.975$) between subjects randomised to the SEMS treatment groups and subjects randomised to non-SEMS therapies (*Table 44*).

Grip strength

There was a decline in grip strength with all treatments, but there were no differences between treatment groups or subgroups (*Figure 21*). There were no differences between groups at baseline (ANOVA $\Sigma^2 = 205.7$, 3 df, $F = 0.992$, $p = 0.398$) or at 6 weeks (ANOVA $\Sigma^2 = 51.9$, 3 df, $F = 0.330$, $p = 0.804$). Similarly, there were no significant differences at baseline ($p = 0.555$) or at 6 weeks ($p = 0.569$) between treatment arms (SEMS and non-SEMS therapies) (*Table 45*).

Quality of life

Several quality of life questionnaires were used in the study. These were analysed separately.

QL index

Analysis was based only on subjects who provided outcome data at 6 weeks.

There was a general decline in scored quality of life in all subjects over time, with brief recovery of values at the 6-week assessment (*Figure 22*). The data suggested some baseline imbalance between treatment groups at baseline, which was confirmed by analysis.

QL index: baseline

Baseline imbalance was present at the 10% level by an analysis of variance (ANOVA $\Sigma^2 = 19.3$, 3 df,

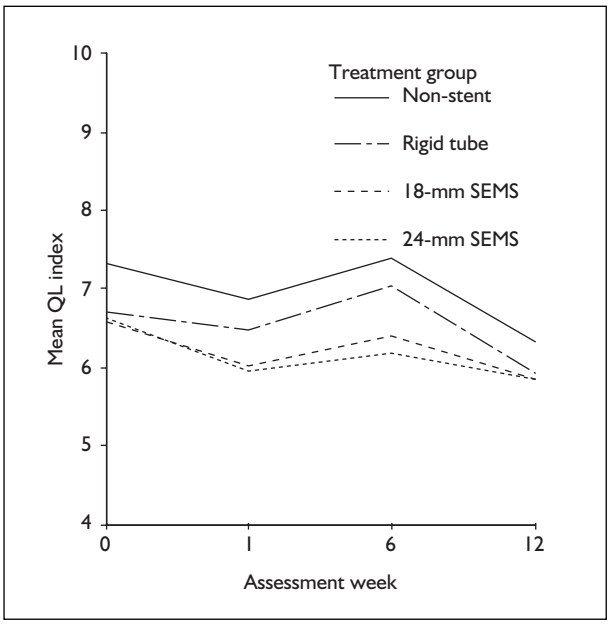

FIGURE 22 *QL index by time and treatment subgroup*

TABLE 46 *Mean QL index at baseline for treatment subgroups*

Treatment group	Mean QL index ± SD
Non-stent	7.77 ± 1.46
Rigid tube	7.23 ± 1.65
18-mm SEMS	6.74 ± 1.91
24-mm SEMS	7.00 ± 1.63

TABLE 47 *Mean QL index at 1 week for treatment subgroups*

Treatment group	*n*	Mean QL index ± SD
Non-stent	34	7.56 ± 1.85
Rigid tube	35	7.31 ± 1.55
18-mm SEMS	32	6.28 ± 2.20
24-mm SEMS	32	6.06 ± 2.20
Total	133	6.83 ± 2.04

$F = 2.33$, $p = 0.077$), owing to a lower QL index at baseline in the groups treated with metal stents ($p = 0.032$) (*Table 46*).

QL index at 1 week

At the 1-week assessment there was a significant difference in QL index between the treatment groups (ANOVA $\Sigma^2 = 54.7$, 3 df, $F = 4.76$, $p = 0.003$) (*Table 47*), which remained significant at the 2% level after allowing for the baseline imbalance, with the baseline QL index value shown to be a significant predictor of the 1-week value (*Table 48*). Comparison of SEMS and non-SEMS treatments at baseline imbalance confirmed a significant difference ($p = 0.002$) (*Table 49*).

QL index at 6 weeks

At 6 weeks the difference between groups was bordering on significance (ANOVA $\Sigma^2 = 33.7$, 3 df, $F = 2.33$, $p = 0.078$) (*Table 50*); however, this was no longer significant after compensating for baseline imbalances, as shown in an analysis of covariance (*Table 51*). Comparison of SEMS and non-SEMS treatment arms is appreciated on the plot of QL index shown in *Figure 23*. Despite the baseline imbalance that was present the plots appeared to diverge. A simple *t*-test analysis also suggested this (*Table 52*). This difference was significant at the 2% level and analysis of covariance was necessary to adjust for the baseline imbalance (*Table 53*). The result remained significant ($p = 0.026$) after adjustment.

The estimate of effect size is shown in *Table 54*. By adding baseline quality of life as a covariate the estimated mean difference in quality of life between those with SEMS and those treated by other means dropped from 0.96 to 0.79, but was still significant at the 5% level. The 95% CI for the effect was +0.09 to +1.48.

From the plots it appears as though the largest difference between the SEMS patients and the

TABLE 48 *Analysis of covariance for QL index at baseline*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	182.455236	4	45.613809	15.80	0.0000
Baseline QL index	126.96176	1	126.96176	43.98	0.0000
Random	30.1146633	3	10.0382211	3.48	0.0181
Residual	363.773771	126	2.88709342		
Total	546.229008	130	4.2017616		
No. of observations = 131, $R^2 = 0.3340$, adjusted $R^2 = 0.3129$, root MSE = 1.69914.					

TABLE 49 *Analysis of covariance comparison of SEMS and non-SEMS QL index*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	180.4747	2	90.237349	31.58	0.0000
Baseline QL index	126.592331	1	126.592331	44.30	0.0000
Stent	28.1341269	1	28.1341269	9.85	0.0021
Residual	365.754308	128	2.85745553		
Total	546.229008	130	4.2017616		
No. of observations = 131, R^2 = 0.3304, adjusted R^2 = 0.3199, root MSE = 1.6904.					

TABLE 50 *Mean QL index at 6 weeks for treatment subgroups*

Treatment group	*n*	Mean week 6 QL index ± SD
Non-stent	36	7.39 ± 2.14
Rigid tube	36	7.08 ± 2.12
18-mm SEMS	32	6.25 ± 2.46
24-mm SEMS	34	6.29 ± 2.07
Total	138	6.78 ± 2.23

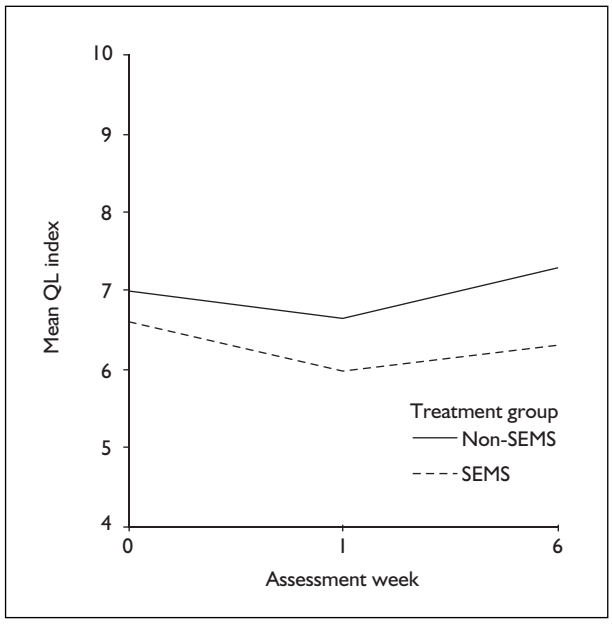

FIGURE 23 *QL index by time and treatment arms*

TABLE 52 *Comparison of mean QL index at 6 weeks for treatment arms*

Treatment group	*n*	Mean QL index ± SD	*t*-Test *p*-value
Non-SEMS	72	7.24 ± 2.12	0.011
SEMS	66	6.27 ± 2.25	

other treatment modalities in terms of QL index was at week 1. This was examined by fitting quality of life at week 1 as a second covariate in the analysis of 6-week scores (*Table 55*). By doing this the difference in QL index at week 6 was no longer significant (difference = 0.31 with 95% CI –0.33 to +0.97) (*Table 56*). It appears that the drop in QL index between baseline and 1 week was greatest for the group that received SEMS, but after that time changes in QL index were broadly similar between the two main two groups.

Karnofsky Performance Scale

Analysis was based on those subjects who provided outcome data at 6 weeks. *Figure 24* indicates that the baseline mean KPS scores were similar across the four treatment groups, and this was confirmed by statistical analysis (ANOVA Σ^2 = 1211.625, F = 1.605, p = 0.191). Subjects treated with non-SEMS therapies had a lower baseline KPS score (p = 0.048), which persisted at week 1, but only at the 6% level (p = 0.057), and when the imbalance at baseline was accounted for this difference was

TABLE 51 *Analysis of covariance for QL index at 6 weeks*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	132.839914	4	33.2099784	8.23	0.0000
Baseline QL index	90.7779999	1	90.7779999	22.49	0.0000
Random	20.1177963	3	6.70593211	1.66	0.1786
Residual	524.760086	130	3661605		
Total	657.60	134	4.90746269		
No observations = 135, R^2 = 0.2020, adjusted R^2 = 0.1775, root MSE = 2.00913.					

TABLE 53 *Analysis of covariance for QL index at 6 weeks*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	132.83601	2	66.4180051	16.71	0.0000
Baseline QL index	92.2173289	1	92.2173289	23.20	0.0000
Stent	20.1138928	1	20.1138928	5.06	0.0261
Residual	524.76399	132	3.97548477		
Total	657.60	134	4.90746269		
No. of observations = 135, R^2 = 0.2020, adjusted R^2 = 0.1899, root MSE = 1.99386.					

TABLE 54 *Estimate of effect size for QL index at 6 weeks*

	QL index week 6	Coefficient	SE	*p*-Value	95% CI	
					Lower	Upper
Constant	2.790657	0.7558707	3.69	0.000	1.29547	4.285844
Baseline QL index	0.50024	0.1038645	4.82	0.000	0.2947858	0.7056943
Stent	0.7861142	0.3494883	2.25	0.026	0.0947918	1.477437

TABLE 55 *Analysis of covariance for QL index at 6 weeks after adjustment for week 1 value*

Source	Partial SS	df	MS	*F*	Prob > *F*
Model	230.876535	3	76.9588451	16.71	0.0000
Residual	407.352472	127	3.20749978		
Total	638.229008	130	4.9094539		
No. of observations = 131, R^2 = 0.3617, adjusted R^2 = 0.3467, $F_{3,127}$ = 23.99, root MSE = 1.7909, Prob > *F* = 0.0000					

TABLE 56 *Estimate of effect size for QL index at 6 weeks after adjustment for week 1 value*

	QL week 6	Coefficient	SE	*p*-Value	95% CI	
					Lower	Upper
Constant	1.672857	0.7129089	2.35	0.020	0.2621388	3.083575
QoL Baseline	0.2003756	0.1088495	1.84	0.068	–0.015018	0.4157692
QoL week 1	0.51795	0.0936459	5.53	0.000	0.3326417	0.7032582
Stent	0.318968	0.3298801	0.97	0.335	–0.333805	0.9717412

TABLE 57 *Mean EQ-5D at time-points for treatment arms*

Assessment	Treatment group	Mean EQ-5D ± SD	Mann–Whitney *U*	Significance
Baseline	SEMS	0.56 ± 0.35	4627.0	0.66
	Non-SEMS	0.56 ± 0.30		
Week 1	SEMS	0.53 ± 0.35	3996.5	0.042
	Non-SEMS	0.46 ± 0.32		
Week 6	SEMS	0.49 ± 0.36	4351.5	0.26
	Non-SEMS	0.45 ± 0.32		

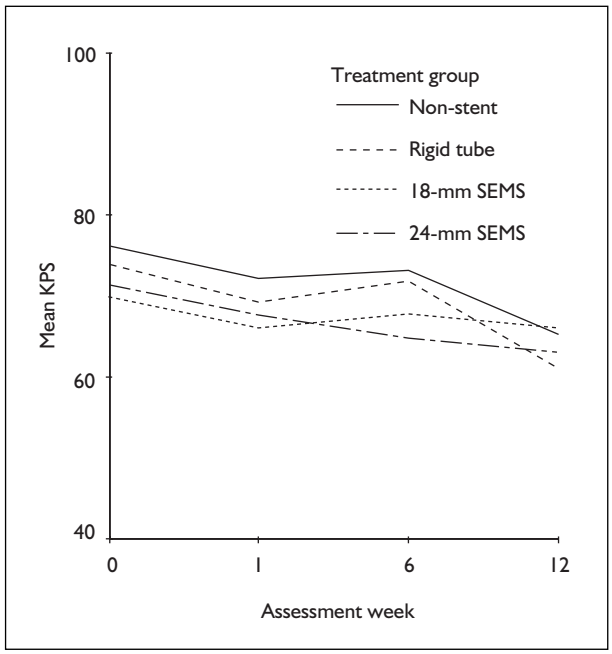

FIGURE 24 *KPS by time and treatment subgroup*

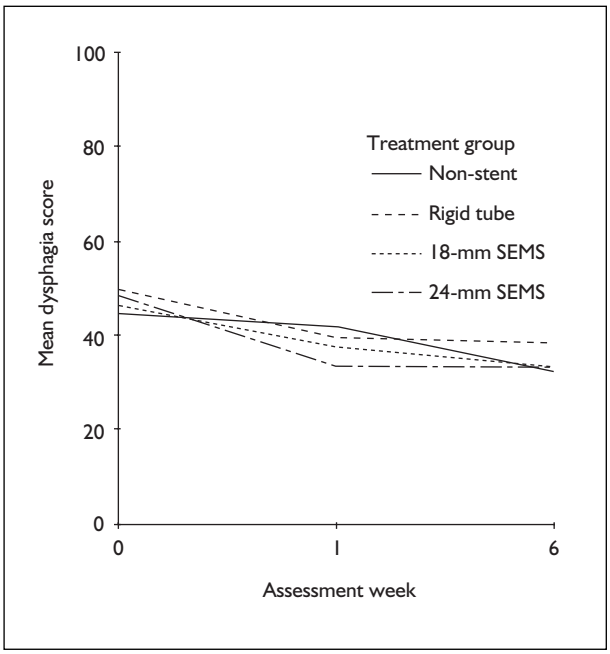

FIGURE 25 *Plot of mean EORTC dysphagia score by time and treatment subgroup*

no longer significant (p = 0.09, 95% CI –0.66 to 8.23).

EuroQol EQ-5D

The EuroQol score is used as part of the cost-effectiveness economic analysis. It is important to determine differences between the main study groups before analysis and whether these correlate with the other quality of life scales. The questionnaire measures health on a cardinal scale from 0 to 1, where by convention 0 = dead and 1 = perfect health. There appears to be a significant difference in mean EQ-5D score between the SEMS and non-SEMS groups at the 1-week assessment, which is not apparent at either baseline or the 6-week assessment (*Table 57*).

EORTC quality of life data analysis

EORTC symptom scales

The generic and modular EORTC quality of life questionnaires are composed of both multi-item and single-item symptom measures which are not repeated in other scales. All data are transformed into a linear range from 0 to 100. The higher the symptom scale score, the worse the problems experienced. For example, a high dysphagia scale score denotes problematic swallowing.

Dysphagia

Three questions are posed regarding the quality of swallowed diet as part of the oesophageal specific EORTC OES24 modular quality of life questionnaire, questions 31–33:

31. Could you eat solid foods?
32. Could you eat liquidised or soft foods?
33. Could you drink liquids?

The scores derived are converted to a linear scale from 0 to 100, where a higher value equates to worse swallowing.

Problems with swallowing were surprisingly rated at low levels (*Figure 25*). The trend was for improvement over time in all groups following treatment, with no significant differences between groups (*Table 58*). Subgroup analysis of the weeks 1 and 6 assessment with regression analysis of covariance verified no differences between treatment groups. The drop in mean EORTC dysphagia scale score from baseline to week 1 was significant at the 1% level (95% CI for mean reduction in dysphagia score –2.6 to –4.1), but the drop in dysphagia score from week 1 to week 6 was not significant (95% CI for change in mean score –7.2 to +2.1).

Deglutition

The deglutition scale is derived from questions 34 and 35 of the OES24 oesophageal module:

34. Have you had problems swallowing your saliva?
35. Have you choked when swallowing?

TABLE 58 *Mean dysphagia score at time-points for treatment arms*

Treatment group	Mean dysphagia score ± SD		
	Baseline	**Week 1**	**Week 6**
Non-SEMS	48.0 ± 25.0	41.7 ± 24.7	35.8 ± 26.0
SEMS	46.6 ± 25.9	36.2 ± 23.9	31.4 ± 26.2
Significance	$p = 0.706$	$p = 0.137$	$p = 0.329$

As for the other symptom scales, the scores are expressed on a linear scale from 0 to 100, where a higher score denotes more problems with deglutition.

Deglutition symptoms were rated very low (*Figure 26*); however, the data were highly skewed owing to the median and modal at all time-points and for all treatments being zero. There were no differences between treatment groups, all of which tended to zero with time, that is, an improvement in deglutition symptoms. Non-parametric analysis of the deglutition variable demonstrated no significant differences between the two main study groups at the three main time-points (baseline: Mann–Whitney $U = 4486.5$, $p = 0.550$; 1 week: Mann–Whitney $U = 3641.0$, $p = 0.429$; 6 weeks: Mann–Whitney $U = 2187.0$, $p = 0.561$) or between subgroups (baseline: $\chi^2 = 1.49$, $p = 0.684$; 1 week: $\chi^2 = 2.62$, $p = 0.454$; 6 weeks: $\chi^2 = 2.73$, $p = 0.435$). Analysis of covariance demonstrated no evidence of any differences between groups at 1 or 6 weeks.

Eating scale

The eating scale is derived from questions 36–39 of the OES24 oesophageal module:

36. Have you had trouble enjoying meals?
37. Have you felt full up too quickly?
38. Have you had troublesome eating?
39. Have you had troublesome eating in front of your family or other people?

As for the other symptom scales, the scores are expressed on a linear scale from 0 to 100, where a higher score denotes more problems.

Again, there was a downward trend for all groups, which was most marked in the first week following treatment (*Figure 27*). No differences were apparent between the treatment groups and this

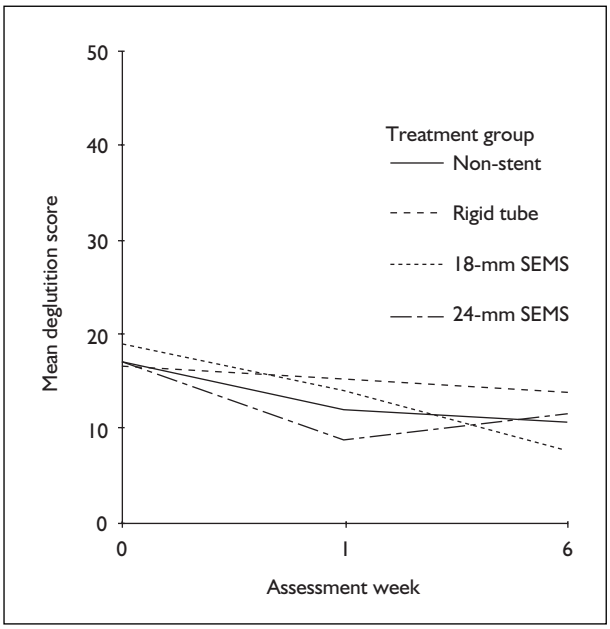

FIGURE 26 *Plot of mean EORTC deglutition score by time and treatment subgroup*

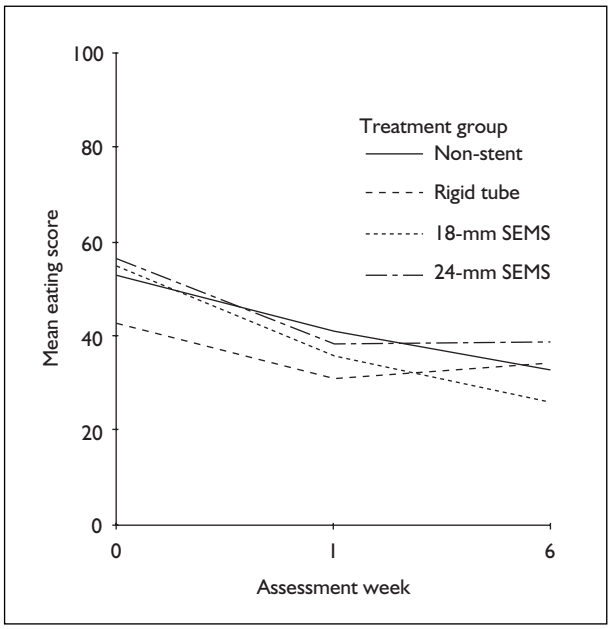

FIGURE 27 *Plot of mean EORTC eating score by time and treatment subgroup*

was confirmed statistically: there were no significant differences between SEMS and non-SEMS groups at the three main time-points (Student's *t*-test: baseline: $p = 0.131$; 1 week: $p = 0.429$; 6 weeks: $p = 0.884$) or between subgroups (ANOVA: baseline $\Sigma^2 = 3808.9$, $F = 1.61$, $p = 0.189$; 1 week: $\Sigma^2 = 1843.2$, $F = 0.75$, $p = 0.523$; 6 weeks: $\Sigma^2 = 2266.5$, $F = 1.14$, $p = 0.336$).

Indigestion score

Three questions are posed regarding indigestion symptoms as part of the oesophageal specific EORTC OES24 modular quality of life questionnaire, questions 44–46.

44. Have you had troublesome belching?
45. Have you had indigestion or heartburn?
46. Have you had trouble with acid or bile coming into your mouth?

The scores derived are converted to a linear scale from 0 to 100, where a higher value equates to more indigestion-like symptoms.

Scores were low, with no apparent differences between the treatment groups (*Figure 28*), and this was confirmed statistically. Analysis of the indigestion variable demonstrated no significant differences between the two main study groups at the three main time-points (Student's *t*-test: baseline: $p = 0.215$; 1 week: $p = 0.115$; 6 weeks: $p = 0.606$) or between subgroups (ANOVA: baseline $\Sigma^2 = 51.639$, $F = 1.72$, $p = 0.163$; 1 week: $\Sigma^2 = 34.0$, $F = 1.18$, $p = 0.319$; 6 weeks: $\Sigma^2 = 4.8$, $F = 0.17$, $p = 0.917$).

Emotional scale

The emotional scale is derived from questions 50–53 from EORTC OES24:

50. Have you worried about your weight being too low?
51. How much has your treatment been a burden to you?
52. How much has your illness been a burden to you?
53. Were you worried about your health in the future?

The scores derived are converted to a linear scale from 0 to 100, where a higher value equates to more anxiety regarding health.

Scores were moderate, equating to some concerns regarding the patients' health (*Figure 29*); however, no significant differences between the treatment groups or study arms were confirmed statistically.

Nausea and vomiting

The nausea and vomiting data were highly skewed, with a considerable proportion of subjects having combined scores of zero. Non-parametric analysis demonstrated no significant differences between SEMS- and non-SEMS-treated patients at any assessment time-point (baseline: Mann–Whitney

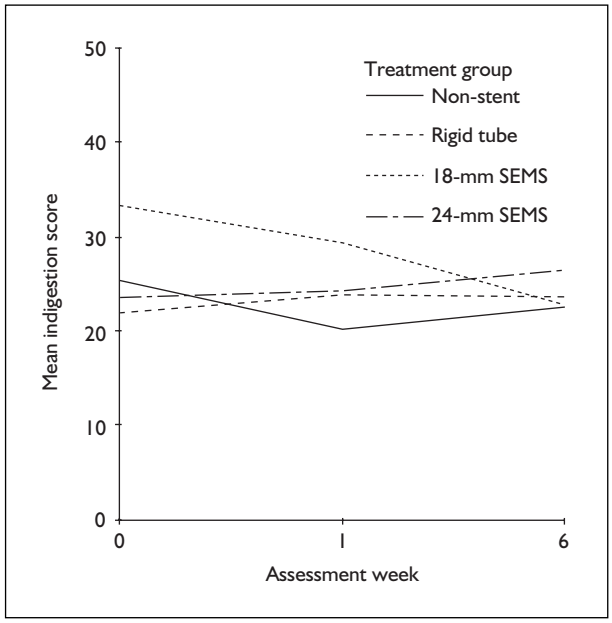

FIGURE 28 *Plot of mean EORTC indigestion score by time and treatment subgroup*

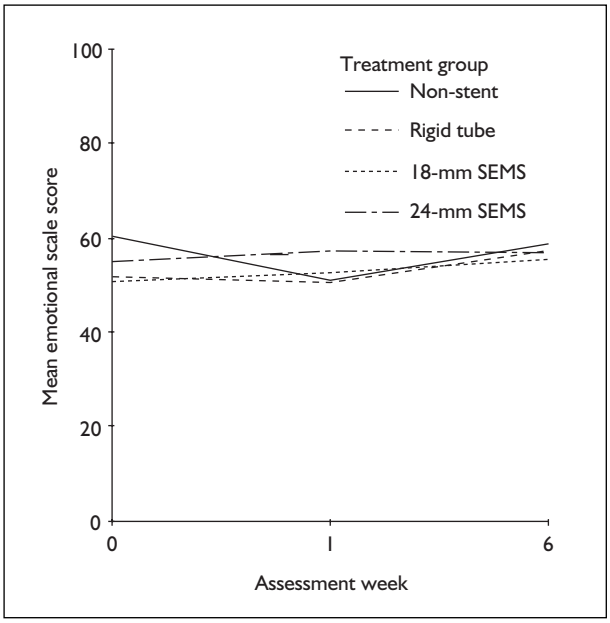

FIGURE 29 *Plot of mean EORTC emotional scale by time and treatment subgroup*

$U = 4214.5$, $p = 0.197$; 1 week: Mann–Whitney $U = 3599.0$, $p = 0.223$; 6 weeks: Mann–Whitney $U = 2040.5$, $p = 0.188$). Similarly, there were no differences between subgroups (baseline: $\chi^2 = 4.16$, $p = 0.245$; 1 week: $\chi^2 = 5.52$, $p = 0.137$, 6 weeks: $\chi^2 = 2.56$, $p = 0.464$). Adjustment for baseline differences using analysis of covariance regression again demonstrated no differences between groups or between SEMS- and non-SEMS-treated patients at the 1 week ($p = 0.54$ and $p = 0.17$, respectively) and 6-week assessments ($p = 0.7824$ and $p = 0.824$, respectively).

Pain

Two pain scores are retrieved from the EORTC questionnaires: the pain symptom scale comes from the generic EORTC QLQ C-30 generic questionnaire, questions 9 and 19:

9. Have you had pain?
19. Did pain interfere with your daily activities?

The pain score is derived from the oesophageal disease-specific OES24, questions 47–49:

47. Have you had pain when you eat?
48. Have you had pain in your chest?
49. Have you had pain in your stomach?

Both scores are expressed on a linear scale from 0–100, with the higher value equating to worse pain. These scores were analysed and evaluated separately.

It appeared that there may be differences between the treatments (*Figure 30*). Both parametric and non-parametric tests confirmed these differences. There were significant differences in the pain scores between groups at the week 1 and week 6 assessments, with generally higher registered pain scores for the stent-type treatments (*Table 59*). *Table 60* shows a comparison of those treated by SEMS and those receiving non-SEMS treatments, again with both parametric and non-parametric tests.

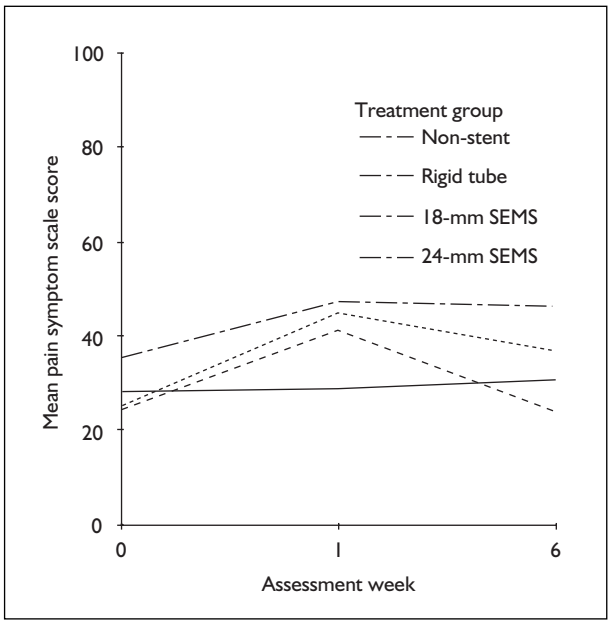

FIGURE 30 *Plot of mean EORTC pain symptom score by time and treatment subgroup*

It appeared that there were significant differences between SEMS and non-SEMS patients at both the week 1 and week 6 assessments with higher pain symptom scores for those patients treated with SEMS.

Adjustment for baseline imbalances using analysis of covariance regression confirmed the difference at 1 week between SEMS- and non-SEMS-treated

TABLE 59 *Mean pain symptom score at time-points for treatment subgroups*

Assessment	Treatment group	Mean pain symptom score ± SD	ANOVA *p*-value	Kruskal–Wallis *p*-value
Baseline	Non-stent	29.3 ± 32.4	0.346	0.454
	Rigid tube	24.4 ± 23.2		
	18-mm SEMS	27.1 ± 27.2		
	24-mm SEMS	34.3 ± 28.4		
Week 1	Non-stent	28.5 ± 28.1	0.01	0.009
	Rigid tube	40.4 ± 26.9		
	18-mm SEMS	45.7 ± 31.9		
	24-mm SEMS	47.6 ± 29.1		
Week 6	Non-stent	30.0 ± 32.0	0.014	0.018
	Rigid tube	24.1 ± 20.7		
	18-mm SEMS	32.8± 24.1		
	24-mm SEMS	44.9 ± 29.9		

TABLE 60 *Mean pain symptom score at time-points for treatment arms*

Assessment	Treatment group	Mean pain symptom score ± SD	*t*-Test *p*-value	Mann–Whitney *U* *p*-value
Baseline	Non-SEMS	26.6 ± 27.8	0.313	0.290
	SEMS	30.7 ± 29.0		
Week 1	Non-SEMS	34.4 ± 28.0	0.006	0.009
	SEMS	46.6 ± 30.5		
Week 6	Non-SEMS	26.9 ± 26.7	0.010	0.009
	SEMS	39.1 ± 27.7		

TABLE 61 *Analysis of covariance for pain symptom score adjusting for baseline imbalance*

Source	SS	df	MS
Model	28031.2049	3	9343.73498
Residual	120909.365	168	719.6986
Total	148940.57	171	870.997484

No. of observations = 172, R^2 = 0.1882, adjusted R^2 = 0.1737, $F_{3,124}$ = 12.98, root MSE = 26.83, Prob > F = 0.0000.

Pain 1	Coefficient	SE	t	*p*-Value	95% CI	
					Lower	Upper
Cons	19.52	6.94	2.81	0.006	5.82	33.22
Pain baseline	0.35	0.07	4.90	0.000	0.21	0.50
Conventional care	15.91	5.77	2.76	0.006	4.52	27.30
Stent	–3.22	5.01	–0.64	0.52	–13.11	6.67

patients (p = 0.008, 95% CI –19.4 to –2.89). Examination of the plots suggested that the most striking difference was that the subjects who received non-stent treatments reported less pain at the week 1 assessment in comparison to the three stent treatments (p = 0.0014), but that the other three subgroups were not statistically different (p = 0.81). As such, it is likely that the observed difference between SEMS and non-SEMS subjects was directly due to the different response of the non-stent patients. This is modelled in *Table 61*.

This model confirmed that the observed difference between SEMS and non-SEMS therapies was explained by the difference between non-stent-treated patients and the other three stent groups. Fitting a model that contained only the non-stent term gave a 95% CI of 8.7 to 27.3 for the difference in mean pain scores at 1 week between SEMS and non-SEMS subjects. The differences at week 6 between SEMS and non-SEMS (95% CI –14.2 to 4.11) and between groups (p = 0.14) were no longer significant, nor was there a difference comparing the non-stent subgroup with the other three stent groups (95% CI for difference in mean pain score –13.1 to 7.8). As such, this analysis was consistent with the

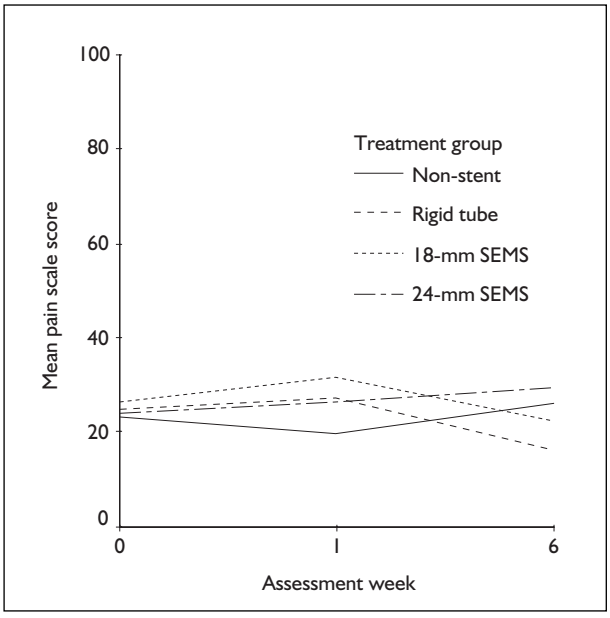

FIGURE 31 *Plot of mean pain scores by time and treatment subgroup*

graphical line plot (*Figure 31*), which suggested that patients in the three stent groups experienced an increase in pain levels at week 1 which had dropped again by week 6 and which the non-stent patients did not experience.

TABLE 62 *Mean pain scores at time-points for treatment subgroups*

Assessment	Treatment group	Mean pain score ± SD	ANOVA *p*-value
Baseline	Non-stent	22.5 ± 22.1	0.65
	Rigid tube	24.6 ± 19.7	
	18-mm SEMS	28.3 ± 22.8	
	24-mm SEMS	26.3 ± 24.9	
Week 1	Non-stent	19.5 ± 20.8	0.052
	Rigid tube	27.8 ± 23.9	
	18-mm SEMS	32.4 ± 21.6	
	24-mm SEMS	28.0 ± 22.9	
Week 6	Non-stent	25.4 ± 23.1	0.285
	Rigid tube	17.5 ± 16.7	
	18-mm SEMS	21.8 ± 19.5	
	24-mm SEMS	25.7 ± 21.4	

TABLE 63 *Comparison of mean pain scores at time-points for treatment arms*

Treatment group	Mean pain score ± SD		
	Baseline	Week 1	Week 6
Non-SEMS	23.6 ± 20.8	23.6 ± 22.6	21.3 ± 20.3
SEMS	27.2 ± 23.8	30.3 ± 22.2	23.8 ± 20.4
Significance	$p = 0.262$	$p = 0.048$	$p = 0.473$

The mean plot of the pain scale score again suggested a difference between the non-stent-treated patients and the other three stent groups. These are compared in *Table 62*, which confirms a difference between the subgroups at week 1. *Table 63* shows a comparison of the two main treatment arms of the study. This *t*-test analysis again confirmed a difference at week 1 between SEMS and non-SEMS treatments. After adjusting for any baseline imbalance using the same covariance regression analysis as for the pain symptom score, this difference became of only borderline significance (between SEMS and non-SEMS at week 1: $p = 0.075$, and between treatment groups at week 1: $p = 0.07$). However, as in the previous analysis, modelling the effect of non-stent treatment confirmed a difference between non-stent- and stent-treated groups ($p = 0.049$). With this term fitted, differences between the remaining groups were not significant. This was consistent with the analysis of the pain symptom scale, but was less marked. No differences were demonstrated at the week 6 assessment between treatment groups or arms of the study.

EORTC functioning scales

The five functional scales are multi-item based and are scored on a linear scale from 0 to 100, where a higher score denotes a high or healthier level of functioning.

Physical functioning

The physical functioning scale is derived from five questions from the EORTC QLQ C-30 generic questionnaire:

1. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase?
2. Do you have any trouble taking a long walk?
3. Do you have any trouble taking a short walk outside of the house?
4. Do you need to stay in bed or a chair during the day?
5. Do you need help with eating, dressing, washing yourself or using the toilet?

There did not appear to be major differences between the groups (*Figure 32*). There were no significant differences between SEMS and non-SEMS treatment groups (*Table 64*). There were no differences between the treatment subgroups, even after adjustment for baseline imbalance using analysis of covariance regression modelling ($p = 0.49$) (*Table 65*).

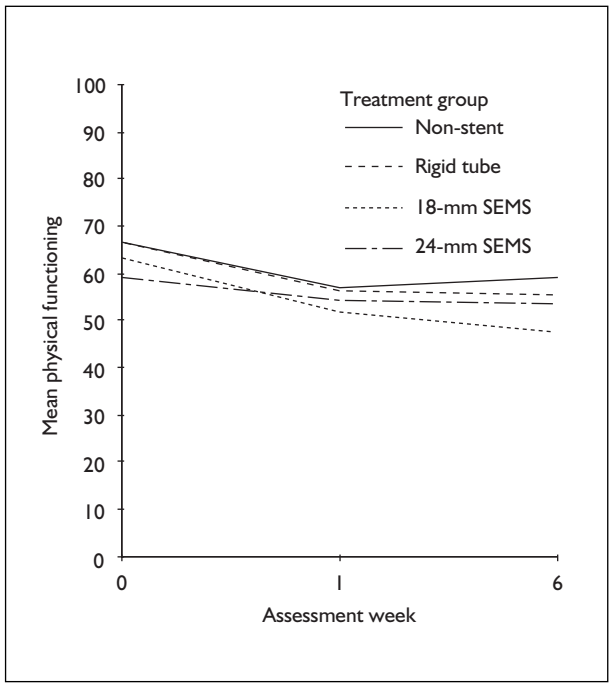

FIGURE 32 *Plot of mean physical functioning scale by time and treatment subgroup*

EORTC emotional functioning

The emotional functioning scale is derived from four items from the EORTC QLQ C-30 generic questionnaire:

21. Did you feel tense?
22. Did you worry?
23. Did you feel irritable?
24. Did you feel depressed?

No differences existed in emotional functioning between SEMS and non-SEMS treated subjects at any time-point, even after adjustment for any baseline differences using analysis of covariance regression modelling ($p = 0.631$) (*Figure 33* and *Table 66*). There were no significant differences between the treatment groups at the three time-points without adjustment for baseline values (*Table 67*); however, after adjustment for imbalances using covariance regression analysis, a difference in the 1-week values between the subgroups at the 6% level was seen ($p = 0.051$). This was due to higher scores for patients treated by 24-mm SEMS (i.e. these patients felt less tense

TABLE 64 *Comparison of mean physical functioning scores for treatment arms*

Assessment	Treatment group	Mean physical functioning score ± SD	*t*-Test *p*-value
Baseline	Non-SEMS	66.0 ± 26.9	0.180
	SEMS	61.0 ± 25.8	
Week 1	Non-SEMS	57.4 ± 25.5	0.241
	SEMS	52.8 ± 26.9	
Week 6	Non-SEMS	57.5 ± 26.5	0.198
	SEMS	51.7 ± 26.0	

TABLE 65 *Comparison of mean physical functioning scores for treatment subgroups*

Assessment	Treatment group	Mean physical functioning score ± SD	ANOVA *p*-value
Baseline	Non-stent	65.8 ± 24.6	0.56
	Rigid tube	66.3 ± 29.0	
	18-mm SEMS	62.4 ± 24.0	
	24-mm SEMS	59.6 ± 26.4	
Week 1	Non-stent	58.6 ± 25.9	0.605
	Rigid tube	56.3 ± 25.2	
	18-mm SEMS	51.3 ± 25.0	
	24-mm SEMS	54.4 ± 29.1	
Week 6	Non-stent	59.6 ± 26.8	0.523
	Rigid tube	55.6 ± 26.4	
	18-mm SEMS	50.2 ± 25.2	
	24-mm SEMS	53.1 ± 27.1	

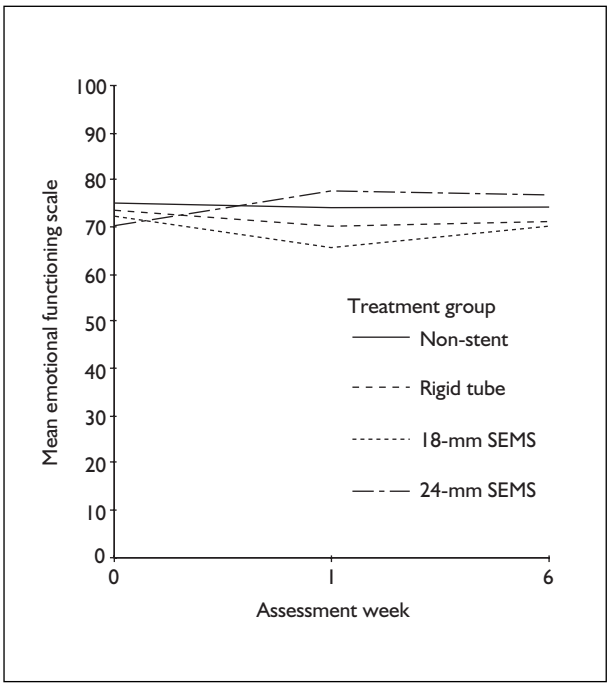

FIGURE 33 *Plot of mean emotional functioning score by time and treatment subgroup*

or worried) and low scores for 18-mm SEMS patients (i.e. these patients felt more tense or worried), which cancelled out in the overall analysis.

Cognitive functioning

The cognitive functioning scale is derived from two items from the EORTC QLQ C-30 generic questionnaire:

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
25. Have you had difficulty remembering things?

A significant difference, at the 3% level, was present between SEMS and non-SEMS patients at week 1 using a parametric test (*Table 68*); however, scores were highly skewed, which is not appreciable on a mean plot (*Figure 34*). As such, non-parametric analysis was performed, which still suggested a difference, albeit at a lower level of significance ($p = 0.06$). After adjustment for baseline differences by analysis of covariance

TABLE 66 *Comparison of mean emotional functioning scores for treatment arms*

Assessment	Treatment group	Mean emotional functioning score ± SD	*t*-Test *p*-value
Baseline	Non-SEMS	74.3 ± 23.0	0.22
	SEMS	70.2 ± 23.7	
Week 1	Non-SEMS	72.4 ± 24.6	0.28
	SEMS	71.3 ± 25.1	
Week 6	Non-SEMS	72.9 ± 23.9	0.85
	SEMS	73.7 ± 26.4	

TABLE 67 *Comparison of mean emotional functioning scores for treatment subgroups*

Assessment	Treatment group	Mean emotional functioning score ± SD	ANOVA *p*-value
Baseline	Non-stent	75.7 ± 22.3	0.58
	Rigid tube	73.1 ± 23.7	
	18-mm SEMS	69.3 ± 23.4	
	24-mm SEMS	71.1 ± 24.9	
Week 1	Non-stent	74.3 ± 24.0	0.10
	Rigid tube	70.6 ± 25.2	
	18-mm SEMS	65.4 ± 26.4	
	24-mm SEMS	78.0 ± 22.1	
Week 6	Non-stent	74.5 ± 24.5	0.95
	Rigid tube	71.3 ± 23.6	
	18-mm SEMS	73.4 ± 27.7	
	24-mm SEMS	74.0 ± 25.5	

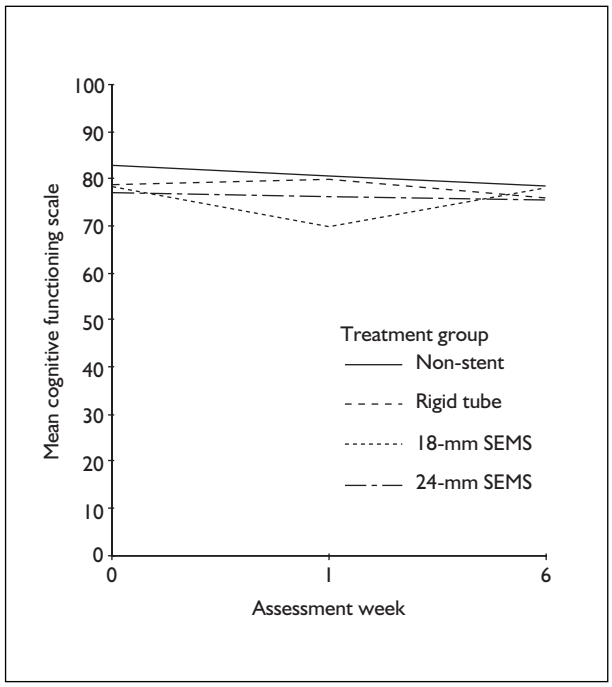

FIGURE 34 *Plot of mean cognitive functioning score by time and treatment subgroup*

regression, this difference at 1 week persisted ($p = 0.032$, 95% CI for mean difference between metal stents and other treatments 0.51 to 11.7). At the week 1 assessment non-SEMS patients reported fewer difficulties in remembering things and concentrating than SEMS-treated patients.

There were no significant differences between the four treatment groups at any time-points using either parametric or non-parametric tests (*Table 69*). Adjustment for baseline imbalance using analysis of covariance regression did not yield any differences ($p = 0.37$).

Role functioning

The role functioning scale is derived from two items from the EORTC QLQ C-30 generic questionnaire:

6. Were you limited in doing either your work or other daily activities?
7. Were you limited in pursuing your hobbies or other leisure time activities?

TABLE 68 *Comparison of mean cognitive functioning scores for treatment arms*

Assessment	Treatment group	Mean cognitive functioning score ± SD	*t*-Test *p*-value	Mann–Whitney *U* *p*-value
Baseline	Non-SEMS	80.6 ± 23.0	0.56	0.76
	SEMS	78.5 ± 25.9		
Week 1	Non-SEMS	80.2 ± 18.7	0.03	0.063
	SEMS	73.2 ± 23.9		
Week 6	Non-SEMS	76.7 ± 25.4	0.84	0.97
	SEMS	75.8 ± 27.0		

TABLE 69 *Comparison of mean cognitive functioning scores for treatment subgroups*

Assessment	Treatment group	Mean cognitive functioning score ± SD	ANOVA *p*-value	Kruskal–Willis *p*-value
Baseline	Non-stent	83.0 ± 23.2	0.75	0.75
	Rigid tube	78.5 ± 22.9		
	18-mm SEMS	79.2 ± 25.1		
	24-mm SEMS	77.9 ± 26.9		
Week 1	Non-stent	80.7 ± 19.4	0.12	0.18
	Rigid tube	79.6 ± 18.1		
	18-mm SEMS	70.9 ± 22.1		
	24-mm SEMS	75.8 ± 25.8		
Week 6	Non-stent	77.1 ± 27.7	0.64	0.77
	Rigid tube	76.3 ± 23.4		
	18-mm SEMS	80.1 ± 22.5		
	24-mm SEMS	71.7 ± 30.5		

There appeared to be significant differences in role functioning scores between SEMS and non-SEMS treatment groups on a mean plot of scores (*Figure 35* and *Table 70*). Parametric analysis confirmed these differences at baseline and the week 1 assessment. However, these differences were not present between the treatment subgroups (*Table 71*), and when baseline imbalances were accounted for, the difference seen at the week 1 assessment between SEMS and non-SEMS therapies was no longer significant ($p = 0.3$, 95% CI –4.35 to 13.5), nor was there a difference at 6 weeks ($p = 0.694$). Similarly, there were no differences between the subgroups in this analysis (week 1: $p = 0.41$; week 6: $p = 0.23$).

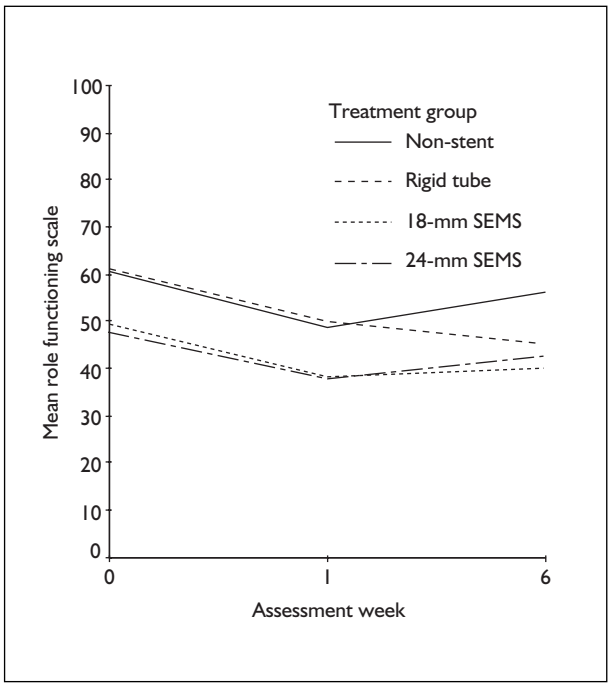

FIGURE 35 *Plot of mean role functioning score by time and treatment subgroup*

Social functioning

The social functioning scale is derived from two items from the EORTC QLQ C-30 generic questionnaire:

25. Has your physical condition or medical treatment interfered with your family life?
26. Has your physical condition or medical treatment interfered with your social activities?

TABLE 70 *Comparison of mean role functioning scores for treatment arms*

Assessment	Treatment group	Mean role functioning score ± SD	*t*-Test *p*-value
Baseline	Non-SEMS	60.6 ± 35.3	0.017
	SEMS	48.3 ± 36.2	
Week 1	Non-SEMS	50.0 ± 33.9	0.03
	SEMS	38.8 ± 34.2	
Week 6	Non-SEMS	49.8 ± 34.4	0.285
	SEMS	43.3 ± 35.9	

TABLE 71 *Comparison of mean role functioning scores for treatment subgroups*

Assessment	Treatment group	Mean role functioning score ± SD	ANOVA *p*-value
Baseline	Non-stent	60.4 ± 34.9	0.128
	Rigid tube	60.9 ± 36.0	
	18-mm SEMS	47.9 ± 33.2	
	24-mm SEMS	48.6 ± 39.2	
Week 1	Non-stent	49.6 ± 37.1	0.195
	Rigid tube	50.4 ± 30.7	
	18-mm SEMS	38.7 ± 32.6	
	24-mm SEMS	38.9 ± 36.2	
Week 6	Non-stent	54.8 ± 37.4	0.472
	Rigid tube	45.1 ± 31.2	
	18-mm SEMS	42.5 ± 34.6	
	24-mm SEMS	44.1 ± 35.2	

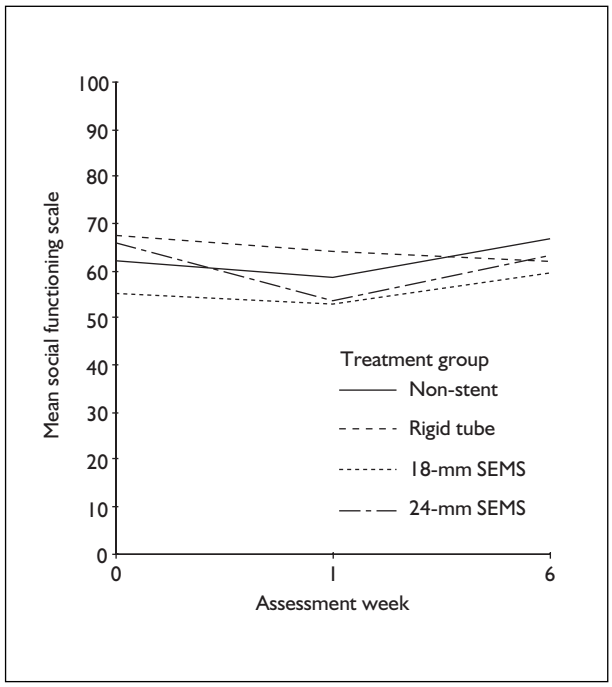

FIGURE 36 *Plot of mean social functioning score by time and treatment subgroup*

There were no differences between SEMS and non-SEMS treatment groups on this analysis (*Figure 36* and *Table 72*). Adjustment for baseline imbalance yielded no additional differences (week 1: $p = 0.171$; week 6: $p = 0.313$). There were no significant differences between subgroups (*Table 73*), even after adjustment for baseline imbalances (week 1: $p = 0.66$; week 6: $p = 0.38$).

Global health status quality of life score

The global health status score is derived from two items from the EORTC QLQ-C30 generic questionnaire:

29. How would you rate your overall health during the past week?
30. How would you rate your overall quality of life during the past week?

There was a borderline difference at week 1 between SEMS and non-SEMS treatments, even after analysis of covariance adjustment for baseline

TABLE 72 *Comparison of mean social functioning scores for treatment arms*

Assessment	Treatment group	Mean social functioning score ± SD	*t*-Test *p*-value
Baseline	Non-SEMS	64.4 ± 30.8	0.319
	SEMS	59.7 ± 34.7	
Week 1	Non-SEMS	61.8 ± 31.0	0.069
	SEMS	53.0 ± 33.2	
Week 6	Non-SEMS	63.7 ± 31.0	0.854
	SEMS	62.8 ± 28.4	

TABLE 73 *Comparison of mean social functioning scores for treatment subgroups*

Assessment	Treatment group	Mean social functioning score ± SD	ANOVA *p*-value
Baseline	Non-stent	61.5 ± 32.1	0.272
	Rigid tube	67.0 ± 29.6	
	18-mm SEMS	54.6 ± 34.9	
	24-mm SEMS	64.6 ± 34.1	
Week 1	Non-stent	58.9 ± 35.3	0.208
	Rigid Tube	64.8 ± 26.1	
	18-mm SEMS	50.7 ± 31.8	
	24-mm SEMS	55.6 ± 34.9	
Week 6	Non-stent	66.2 ± 31.9	0.919
	Rigid Tube	61.4 ± 30.3	
	18-mm SEMS	62.9 ± 27.1	
	24-mm SEMS	62.6 ± 30.0	

differences (p = 0.06, 95% CI –0.33 to 11.89) (*Figure 37* and *Table 74*). There were no differences at 6 weeks (p = 0.70). This implies that patients treated with SEMS therapies reported a lower global quality of life than non-SEMS-managed patients. There were no significant differences between subgroups at any time point and analysis of covariance confirmed this (week 1: p = 0.20; week 6: p = 0.17).

Survival

Broadly similar courses appeared to run for the two main study arm patients over a 2-year period (*Figure 38*). However, there was some divergence of the lines and non-parametric analysis of mean survival in days between these groups suggested a significant advantage for those patients receiving non-SEMS treatments. This advantage approximates to 30 days longer life following treatment for non-SEMS patients (*Table 76*).

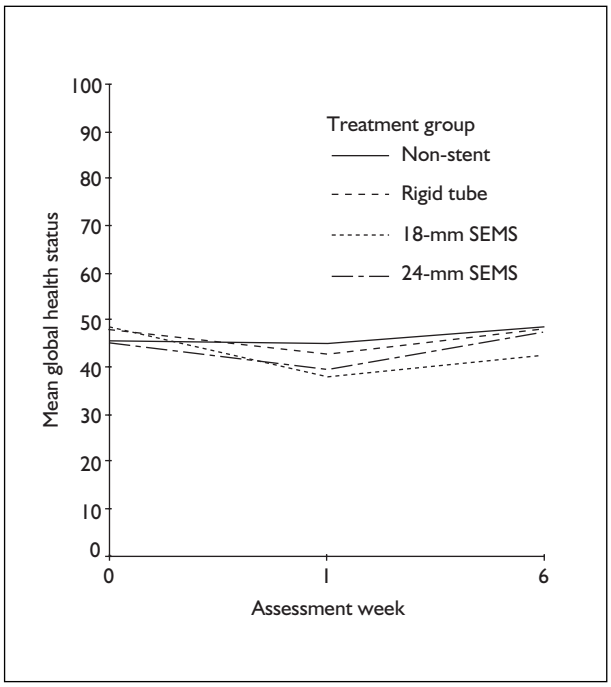

FIGURE 37 *Plot of mean global health status score by time and treatment subgroup*

TABLE 74 *Comparison of mean global health status score by time and treatment arms*

Assessment	Treatment group	Mean global health status score ± SD	*t*-Test *p*-value
Baseline	Non-SEMS	46.7 ± 25.9	0.814
	SEMS	45.8 ± 25.0	
Week 1	Non-SEMS	44.1 ± 21.9	0.077
	SEMS	38.3 ± 21.2	
Week 6	Non-SEMS	47.8 ± 22.8	0.514
	SEMS	45.3 ± 21.4	

TABLE 75 *Comparison of mean global health status score by time and treatment subgroups*

Assessment	Treatment group	Mean global health status score ± SD	ANOVA *p*-value
Baseline	Non-stent	45.2 ± 26.3	0.94
	Rigid tube	48.0 ± 25.7	
	18-mm SEMS	46.3 ± 21.7	
	24-mm SEMS	45.4 ± 28.1	
Week 1	Non-stent	45.3 ± 22.1	0.31
	Rigid tube	42.8 ± 21.9	
	18-mm SEMS	37.5 ± 20.6	
	24-mm SEMS	39.3 ± 21.9	
Week 6	Non-stent	48.3 ± 24.9	0.89
	Rigid tube	47.3 ± 21.0	
	18-mm SEMS	44.1 ± 20.9	
	24-mm SEMS	46.5 ± 22.0	

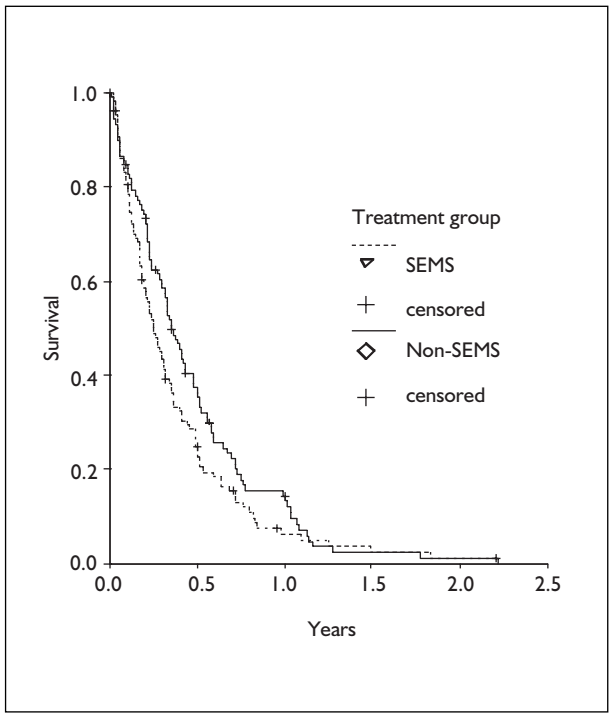

FIGURE 38 *Kaplan–Meier survival plot by treatment arm*

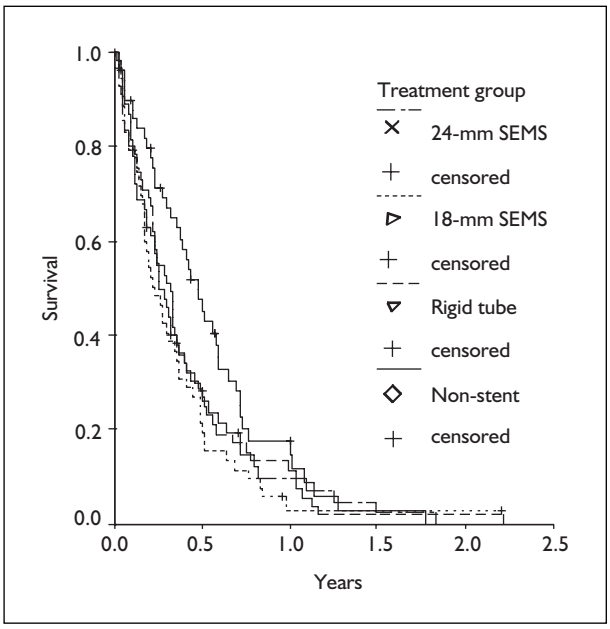

FIGURE 39 *Kaplan–Meier survival plot by treatment subgroup*

TABLE 76 *Comparison of mean survival in days for treatment arms*

Treatment group	Mean survival ± SD (days)	Mean–Whitney *U p*-value
Non-SEMS	162.40 ± 138.78	0.037
SEMS	133.02 ± 135.48	

TABLE 77 *Comparison of mean and median survival in weeks for treatment arms*

Treatment group	Survival	Time (weeks)	SE	95% CI	
				Lower	Upper
Non-SEMS	Mean	24.63	2.16	20.41	28.86
	Median	18.86	1.82	15.29	22.42
SEMS	Mean	20.12	2.09	16.03	24.21
	Median	13.29	1.81	9.74	16.83

TABLE 78 *Statistics for equality of survival distributions between treatment arms*

Test	Test statistic	df	Significance
Log rank	2.89	1	0.0892
Breslow	4.11	1	0.0426

This suggested that a more vigorous and sensitive analysis was justified (*Table 77*). Log-rank analysis indicated a difference in the survival curves for the treatment arms at the 9% level and the Breslow test indicated significance at the 5% level (*Table 78*). This was not conclusive, but there was certainly inequality between the groups and, therefore, subgroup analysis was performed to determine whether one of the subgroups was responsible for the difference. A Kaplan–Meier plot of the subgroup survival curves (*Figure 39*) suggest that the previously identified difference between SEMS and non-SEMS treatments may stem from patients in the non-stent subgroup, with the three stent subgroups exhibiting equal survival characteristics. Cox regression analysis with a likelihood ratio test as inclusion criterion was carried out to determine whether the variables listed in *Table 79* were predictors of time to death. As noted in the previous analysis, the difference between treatment groups was of borderline significance (12% level). This would not usually justify further exploration of the groups but, in

TABLE 79 *Cox regression analysis*

Variable	Score	df	Significance
Gender	2.436	2	0.296
Treatment group	5.842	3	0.12
Non-stent	4.779	1	0.029
Radiotherapy	1.175	1	0.278

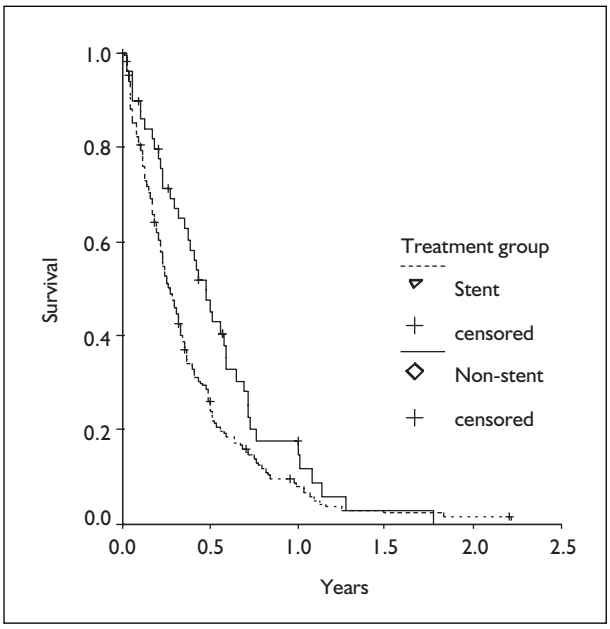

FIGURE 40 *Kaplan–Meier survival plot comparing non-stent and stent patients*

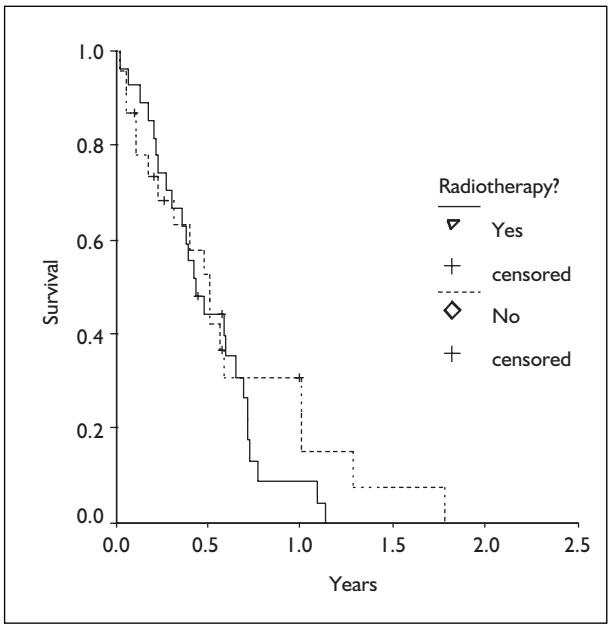

FIGURE 41 *Kaplan–Meier survival plot for radiotherapy and non-radiotherapy patients from the non-stent treatment subgroup*

view of the findings from the survival curves, further evaluation of the non-stent patients to the three other stent subgroups demonstrated a significant difference at the 3% level. This can be demonstrated on a Kaplan–Meier plot (*Figure 40*). The curves are in *Figure 40* clearly divergent in their course, with a survival advantage for patients receiving non-stent treatments. A common-sense assumption would be that this survival advantage was due to the cytotoxic effect of radiotherapy, as approximately half of the non-stent group were treated in this fashion; however, the Cox regression suggested otherwise, as there was no demonstrable significant difference between those receiving radiotherapy and the other subjects. Despite the small number, this is made apparent when graphically represented (*Figure 41*). As such, there was no evidence that radiotherapy had an effect on survival in this subgroup (*Table 80*), but as a whole the non-stent patients had a small but significant survival advantage over stent patients, regardless of the use of rigid tube or SEMS.

TABLE 80 *Test statistics for equality of survival distributions between radiotherapy and non-radiotherapy patients in the non-stent treatment subgroup*

Test	Test statistic	df	Significance
Log-rank	0.11	1	0.735
Breslow	0.29	1	0.590

Mortality

There were no significant differences in the in-hospital mortality (χ^2 = 1.34, 3 df, p = 0.720) or 30-day mortality (χ^2 = 4.86, 3, df, p = 0.182) between treatment subgroups or study arms (in-hospital: χ^2 = 0.0987, 1 df, p = 0.753; 30-day: χ^2 = 0.786, 3 df, p = 0.375). Seventeen patients died in hospital following treatment during their initial admission (*Table 81*). The median time from admission to death was 12 days (range 5–31).

The causes of death are detailed in *Table 82*. There were no differences in the causes of death between treatment arms or subgroups. The two most common causes of death in hospital were a rapid and unexplainable deterioration in condition following treatment, and aspiration pneumonia, which together accounted for 71% of all in-hospital mortality (n = 12). Thirty-two patients died within 30 days of primary treatment, including all but one of the in-hospital deaths.

TABLE 81 *In-hospital and 30-day mortality for treatment subgroups*

Treatment group	*n*	In-hospital mortality	30-day mortality
Non-stent	47	3	3
Rigid tube	52	6	10
18-mm SEMS	51	5	11
24-mm SEMS	53	3	7

TABLE 82 *Cause of death for in-hospital mortality*

Cause of in-hospital deaths	*n*
General deterioration	7
Aspiration pneumonia	5
Myocardial infarction	2
Perforation	1
Massive bleed	1
Cerebrovascular accident	1

TABLE 83 *Cause of death for 30-day mortality*

Cause of death	*n*
General deterioration	14
Massive bleed	6
Aspiration pneumonia	5
Myocardial infarction	2
Perforation	2
Migration	1
Pulmonary embolus	1
Cerebrovascular accident	1

Similarly, there were no significant differences in the 30-day causes of death (*Table 81*). No specific cause of death, other than the underlying oesophageal malignancy, was found in 14 patients (44%), with an unexplainable deterioration in physical condition following treatment (*Table 83*). Massive upper gastrointestinal haemorrhage and aspiration pneumonia were the most common specified causes of death and occurred equally between groups. It is likely that concealed haemorrhage or aspiration accounted for many of the unexplained deaths.

Complications

Data on overall mortality and morbidity rates are shown in *Table 84*.

Early complications

Early complications were common with all treatments, affecting 37% of patients ($n = 78$) (*Table 85*). There were no differences between groups except in the incidence of total dysphagia after treatment, which occurred almost exclusively in the non-stent group: six cases occurred in patients who had received BICAP or ETN treatment and one case in a patient treated with intraluminal radiotherapy. In overall terms, aspiration was relatively uncommon (2%) following treatment and only occurred in patients who had a stent placed across the oesophagogastric junction, but as 91 patients were treated in this manner this accounted for one in 20 oesophagogastric stent placements (5.5%), with all cases resulting in death. Three perforations occurred after treatment (1.4%), one of which was fatal. All perforations occurred with different treatments: one as a result of dilatation before brachytherapy and the other two after stenting. Two further perforations occurred as late events, but were felt to be due to spontaneous tumour perforation rather than as a result of treatment. Fifteen stents (7%) migrated immediately after placement or within the first 2 weeks and these occurred equally between the stent therapies. All migrations were distal and none required removal of the displaced stent. Nine patients (4%) had problematic bleeding following treatment requiring transfusion. Thirty-five patients (16.8%) had severe, disabling pain requiring hospitalisation and opiates after treatment, with no significant differences in incidence between treatment groups.

Late complications

Between SEMS and non-SEMS therapies there were no differences in late complications other than the late migration rate (overall 10%) (*Table 86*). This was significantly higher in the non-SEMS arm of the study (18%), which included primary rigid intubation and also secondary salvage stent treatment for failed non-stent patients. In comparison, SEMS rarely migrated when placed as a primary treatment (3%). Food bolus obstruction and tumour overgrowth

TABLE 84 *Overall mortality and morbidity rates by treatment arm*

Complication	Treatment arm		*p*-Value
	Non-SEMS ($n = 99$)	SEMS ($n = 104$)	
In-hospital mortality	9 (9%)	8 (8%)	ns
Early complications	36 (36%)	42 (40%)	ns
Late complications	56 (57%)	31 (30%)	< 0.001

ns, not significant.

TABLE 85 *Early complications*

Complication	Non-SEMS		SEMS		SEMS vs non-SEMS *p*-value
	Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS	
None	30	36	36	30	ns
Technical failure	0	1	1	1	ns
Severe pain	7	8	8	12	ns
Total dysphagia	7	0	0	1	0.003
Aspiration	0	2	1	2	ns
Migration	0	6	3	6	ns
Bleeding	3	0	4	2	ns
Perforation	1	1	0	1	ns
n	47	52	51	53	

TABLE 86 *Late complications*

Complication	Non-SEMS		SEMS		SEMS vs non-SEMS *p*-value
	Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS	
Overgrowth	2	7	4	1	ns
Bleeding	3	12	11	3	ns
Migration	8	11	2	1	0.0002
Aspiration	0	0	2	2	ns
Stricture	1	0	0	0	ns
Perforation	0	1	0	1	ns
Food bolus obstruction	2	9	2	2	ns
n	47	52	51	53	

TABLE 87 *Unscheduled retreatment*

	Non-SEMS		SEMS	
	Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS
Total no. of patients	47	52	51	53
No. of patients having one treatment only	6	32	36	34
No. of unscheduled additional treatment	86	36	20	29
Non-stent	50	23	10	18
Rigid intubation	8	4	1	0
SEMS	28	9	9	11

accounted for late obstructions. Overgrowth occurred in 14 patients (6%), two in salvage stents following failure of non-stent treatment. Food bolus obstruction was higher in the rigid tube treatment subgroup ($\chi^2 = 9.28$, 3 df, $p = 0.026$). Thirty-seven patients (9%) developed problematic bleeding requiring blood transfusion, with no difference between the main study arms, but this was significantly more common in the rigid tube and 18-mm SEMS subgroups. Aspiration was uncommon as a late pathology, occurring in four SEMS-treated patients. Only one of 26 primary radiotherapy-treated patients (4%) developed a post-treatment fibrous stricture; this patient had received a local brachytherapy boost in addition to primary EBRT.

Retreatment

Many patients in the non-stent subgroup required scheduled repeated treatment, such as a course of ten fractionated doses of EBRT or a couple of planned APC sessions. However, there is a significant difference between treatment arms ($\chi^2 = 17.04$, 1 df, $p < 0.001$) and between subgroups ($\chi^2 = 41.06$, 3 df, $p < 0.001$) in terms of the number of patients who only required one palliative treatment, be that one stent treatment or one course of APC (*Table 87*). This is largely due to

TABLE 88 *Unscheduled endoscopies with or without dilatation*

	Non-SEMS		SEMS	
	Non-stent	Rigid tube	18-mm SEMS	24-mm SEMS
Total no. of patients	47	52	51	53
Unscheduled pretreatment endoscopy + dilatations	7	1	0	0
Unscheduled posttreatment endoscopy + dilatations	31	2	3	3
Unscheduled endoscopy	19	38	9	12

the non-stent subgroup patients, who required a greater number of both non-stent and stent treatments following initial 'definitive' treatment to relieve recurrent symptoms of dysphagia.

Endoscopic dilatation was frequently performed as part of the therapeutic protocol before definitive treatment, for example to allow passage of the endoscope before laser therapy or the passage of the SEMS delivery system. However, while awaiting palliation some patients required separate unscheduled endoscopic dilatation for temporary dysphagia relief (*Table 88*). No patients in the SEMS arms of the study required an unscheduled dilatation, but eight such dilatations were necessary in non-SEMS patients ($p = 0.003$), seven of which occurred in the non-stent subgroup ($p < 0.001$). Similarly, dilatation after definitive treatment was rarely required for stent treatments, but was common in the non-stent patients ($\chi^2 = 86.19$, 3 df, $p < 0.001$). As a rule, unscheduled endoscopic examination of the oesophagus without dilatation was required when symptoms recurred, to check the status of the tumour, to clear food boluses or to reposition migrated stents. This was more frequently required in the non-SEMS patients ($\chi^2 = 41.36$, 3 df, $p < 0.001$) and most frequently required in patients who received treatment by rigid intubation ($\chi^2 = 35.48$, 1 df, $p < 0.001$).

Health state utilities

When the inclusion criteria were applied to the list of 112 potential participants, 71 patients (63%) were eligible. Of the 71 patients, three (4%) did not respond. This gave 68 interviews, of which 12 (18%) were not completed owing to serious health concerns or for personal reasons. Complete data were therefore obtained from 56 participants, giving a 79% response rate: 28 were randomised to the TTO group and 28 to the SG group. The mean age of participants was 68 ± 7.6 years, with a male to female ratio of 2:1 (39 men and 17 woman), which is representative of the UK oesophageal cancer population.[1,17] The EQ-5D scores indicate that the study population was in poorer health than a cross-section of the UK population.[18] Consistency rankings were high, with 52 participants (93%) ranking the health state scenarios appropriately. Four participants (14%) who ranked inconsistently were excluded from further statistical analysis.

The health state valuations were in accordance with theoretical validity (*Table 89* and *Figure 42*). TTO and SG health state values for the better health states were higher than the values for the worse health states (TTO: $F_{4,98} = 30.0$, $p < 0.001$; SG: $F_{4,108} = 53.8$; $p < 0.001$). TTO states generated higher mean values than SG for scenarios 1 and 2, and SG generated higher mean values for scenarios 3 and 4, but observed differences were not statistically significant. Both TTO and SG had the same mean value for the worst ranked health state, 5.

Treatment scenarios were rated similarly between the two valuation methods (*Table 90* and *Figure 43*). Comparisons within both TTO and SG demonstrated highly statistically significant

TABLE 89 *Comparison between TTO and SG health state valuations*

Health state scenario	TTO: mean (95% CI)	SG: mean (95% CI)	Difference (95% CI)	*t*-Statistic (*p*-value)
1	0.66 (0.50 to 0.81)	0.78 (0.66 to 0.89)	0.12 (–0.07 to 0.30)	1.26 (0.21)
2	0.45 (0.31 to 0.60)	0.49 (0.35 to 0.63)	0.04 (–0.15 to 0.23)	0.42 (0.67)
3	0.35 (0.21 to 0.50)	0.27 (0.15 to 0.40)	–0.08 (–0.27 to 0.11)	0.88 (0.39)
4	0.25 (0.13 to 0.38)	0.20 (0.08 to 0.31)	–0.06 (–0.22 to 0.11)	0.69 (0.49)
5	0.08 (–0.00 to 0.17)	0.08 (0.01 to 0.17)	0.01 (–0.11 to 0.12)	0.13 (0.90)

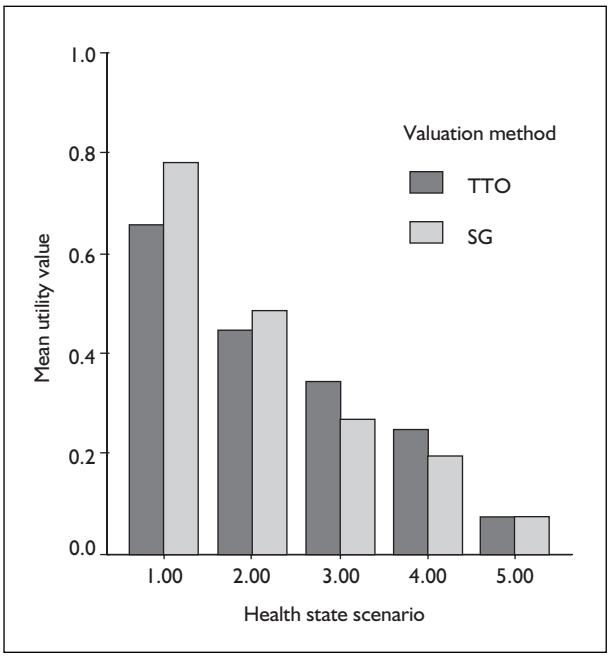

FIGURE 42 *Health state valuation by utility method*

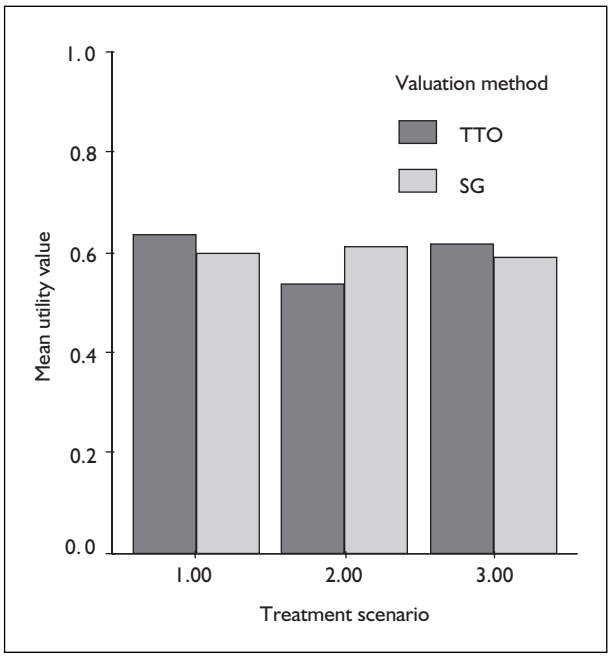

FIGURE 43 *Treatment scenario valuation by utility method*

TABLE 90 *Comparison between TTO and SG treatment valuations*

Health state scenario	TTO: mean (95% CI)	SG: mean (95% CI)	Difference (95% CI)	t-Statistic (*p*-value)
1	0.64 (0.50 to 0.78)	0.60 (0.47 to 0.74)	–0.03 (–0.22 to 0.16)	0.32 (0.75)
2	0.54 (0.40 to 0.69)	0.61 (0.48 to 0.74)	0.07 (–0.12 to 0.26)	0.76 (0.45)
3	0.62 (0.50 to 0.76)	0.59 (0.45 to 0.74)	–0.03 (–0.22 to 0.16)	0.31 (0.76)

differences for the health scenarios (*Table 91*), and although there were no overall significant differences within TTO and SG values for the treatment scenarios, participants demonstrated clear individual treatment preferences (*Table 92*). Initial observation of the data suggests no particular preference for one treatment (*Table 93*), with an approximately equal split between all three scenarios as the most preferred treatment: treatment 2 had the highest value (0.61), followed by treatment 1 (0.60) and lastly treatment 3, which had the lowest value (0.59). However, analysis of the aggregate rankings shows a significant preference for treatment 1 (χ^2 = 34.5, 4 df, $p < 0.0001$). This is best understood by an imaginary scoring system, with 3 points for first choice, 2 for second and 3 for third. Using this method results in 127 points for treatment 1 (stent), 102 for treatment 2 (brachytherapy) and 107 for treatment 3 (thermal ablation).

Costs

The cost data are split into four cost areas: initial, intervention, hospital stay and total cost. Initial cost comprises all costs incurred during the initial palliative treatment and associated hospital stay. Intervention costs are the summation of the costs of all interventions from time of randomisation to death. The hospital stay cost includes all inpatient and outpatient attendances. Total cost is the intervention cost plus the hospital stay cost and thereby includes all initial costs within these parameters. A boxplot suggests differences between the treatment arms in terms of mean initial costs (*Figure 44*). However, the mean total costs appear broadly similar (*Figure 45*). This discrepancy is probably due to the difference in the initial intervention costs of the SEMS, which are considerably higher than those of the non-SEMS groups. However, over time this initial intervention cost is diminished by later

TABLE 91 *Comparison between health scenario values within TTO and SG*

Health scenario comparison	TTO		SG	
	Mean difference (95% CI)	**Paired *t*-statistic (*p*-value)**	**Mean difference (95% CI)**	**Paired *t*-statistic (*p*-value)**
1 vs 2	0.23 (0.12 to 0.35)	4.25 (<0.001)	0.29 (0.16 to 0.41)	4.97 (<0.001)
2 vs 3	0.11 (0.05 to 0.16)	4.48 (<0.001)	0.22 (0.12 to 0.31)	4.70 (<0.001)
3 vs 4	0.10 (0.02 to 0.18)	2.75 (0.011)	0.08 (0.02 to 0.13)	2.96 (0.006)
4 vs 5	0.17 (0.06 to 0.28)	3.40 (0.002)	0.11 (0.02 to 0.19)	2.75 (0.011)

TABLE 92 *Comparison between treatment scenario values within TTO and SG*

Health scenario comparison	TTO		SG	
	Mean difference (95% CI)	**Paired *t*-statistic (*p*-value)**	**Mean difference (95% CI)**	**Paired *t*-statistic (*p*-value)**
1 vs 2	0.10 (–0.03 to 0.22)	1.62 (0.12)	–0.01 (–0.05 to 0.04)	0.26 (0.80)
2 vs 3	–0.08 (–0.20 to 0.04)	1.40 (0.17)	0.02 (–0.05 to 0.08)	0.57 (0.57)
1 vs 3	0.02 (–0.05 to 0.08)	0.52 (0.61)	0.01 (–0.04 to 0.05)	0.34 (0.74)

TABLE 93 *Treatment scenario ranking*

Treatment scenario	Frequency
1st preferred 1	19 (34%)
1st preferred 2	18 (32%)
1st preferred 3	19 (34%)
2nd preferred 1	33 (59%)
2nd preferred 2	10 (18%)
2nd preferred 3	13 (23%)
3rd preferred 1	4 (7%)
3rd preferred 2	28 (50%
3rd preferred 3	24 (43%)

intervention costs and by hospital stay costs (*Figures 46* and *47*).

The mean total intervention cost is approximately £1500 for both treatment arms, whereas the approximate mean hospital stay costs are double this figure. Since total cost is based on intervention plus hospital stay costs, the hospital stay component contributes the majority (60%) of total cost. As hospital stay costs of the arms are broadly similar, this evens out observed differences between groups in initial intervention costs when

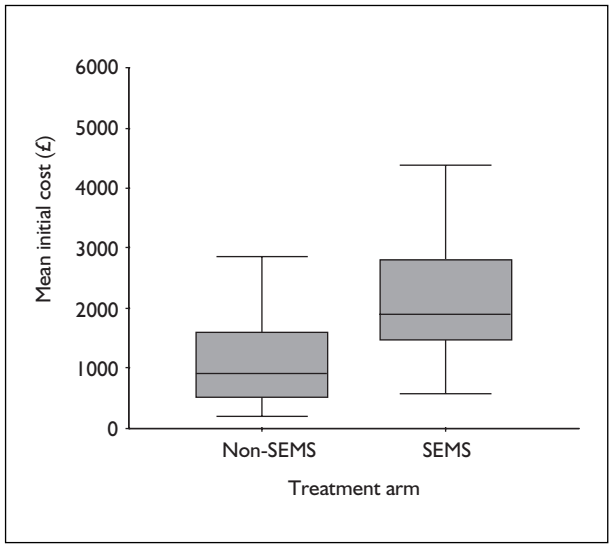

FIGURE 44 *Mean initial cost by treatment arm*

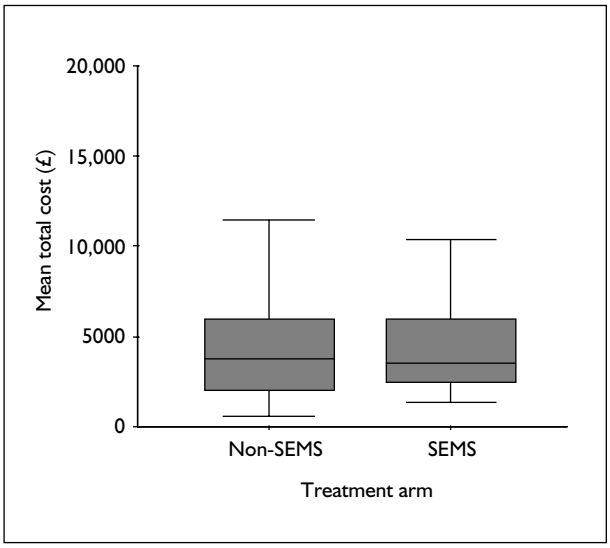

FIGURE 45 *Mean total cost by treatment arm*

the total costs are calculated. Furthermore, despite observed mean value differences, when total cost histograms are plotted for the treatment arms, the data are seen to be highly skewed by outlying values (*Figures 48* and *49*). As such, parametric analysis of means may be inaccurate. Therefore, data were transformed to log mean values before statistical analysis (*Table 94*). Analysis confirms the suspected differences between SEMS and non-SEMS treatment groups, with initial and interventional costs being higher in SEMS patients, but no differences between study groups in hospital stay or total costs.

Sensitivity analysis

The eight highest unit cost variables were selected for the sensitivity analysis. These parameters divided into two well-defined groups: four palliative treatment costs (SEMS, rigid intubation, APC/laser and brachytherapy) and the four most frequently used inpatient beds (surgical, medical and elderly care wards, and medical hospice care ward stay). The midpoint value of each of these variables was varied by 25% around the baseline value, and the lower and upper values obtained were used to calculate new mean total costs for the two main treatment groups, which were again compared for differences using non-parametric analysis. A plot of the new upper and lower mean total cost estimates for both groups suggests that the total costs for non-SEMS treatments are lower (*Figure 50*), however, despite the apparent differences observed the scale of this graph is small and the confidence intervals for these point values (not demonstrated) were wide.

The *y* axis demonstrates the total cost in pounds. The *x* axis comprises the eight treatment cost variables. Variables followed by 1 are the low and high estimates for the SEMS treatment arm when the cited parameter is varied, and variables

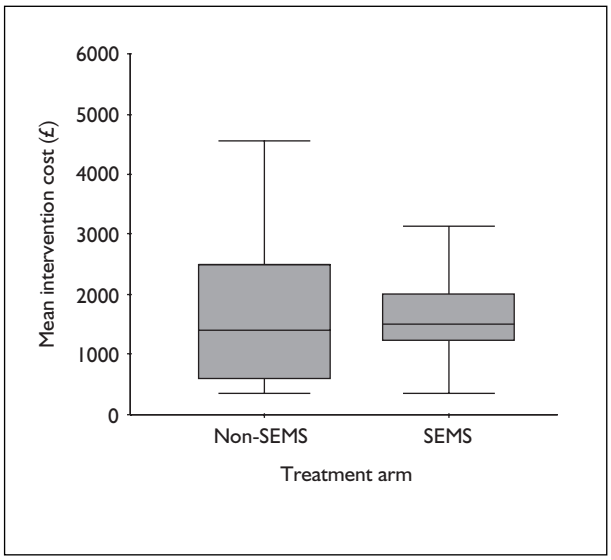

FIGURE 46 *Mean total intervention cost by treatment arm*

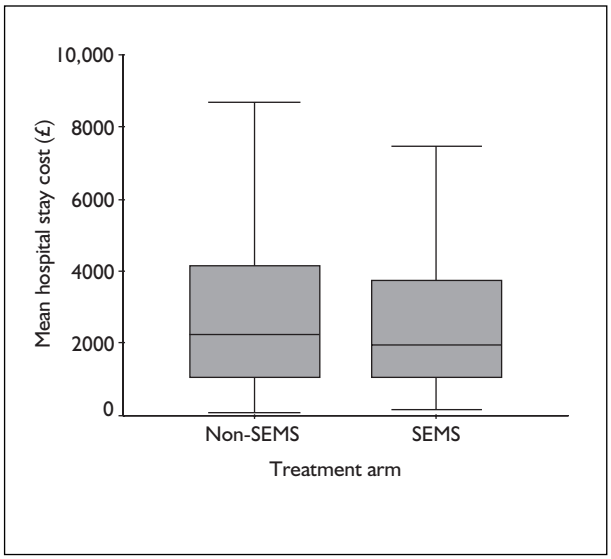

FIGURE 47 *Mean hospital stay cost by treatment arm*

TABLE 94 *Comparison of log cost values by treatment arm*

Cost analysis	Treatment group	Mean ± SD	*t*-Test *p*-value	Mann–Whitney *U* *p*-value
Log initial-cost	Non-SEMS SEMS	6.95 ± 0.76 7.64 ± 0.43	0.001	0.000
Log intervention-cost	Non-SEMS SEMS	7.14 ± 0.83 7.42 ± 0.41	0.003	0.023
Log hospital cost	Non-SEMS SEMS	7.62 ± 1.07 7.54 ± 1.03	0.56	0.498
Log total cost	Non-SEMS SEMS	8.19 ± 0.84 8.26 ± 0.63	0.50	0.760

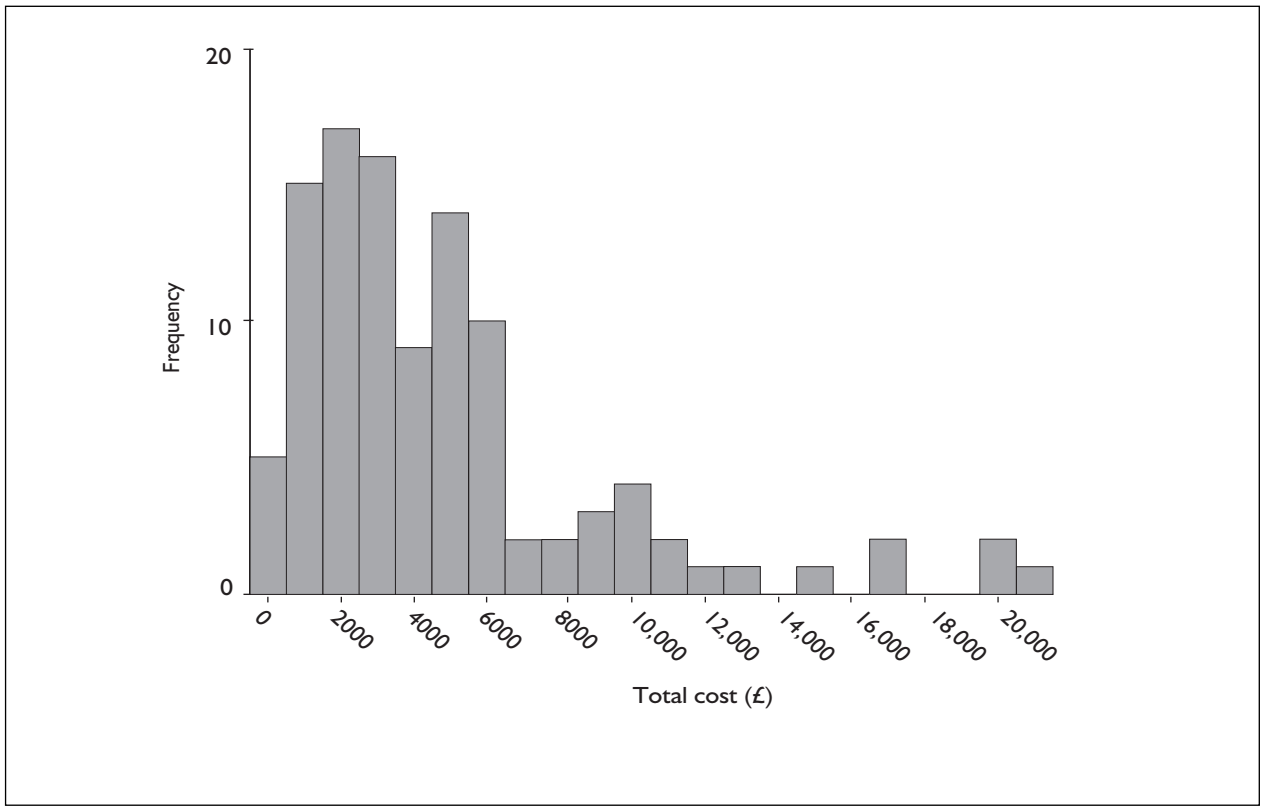

FIGURE 48 *Histogram of spread of total cost values for non-SEMS patients*

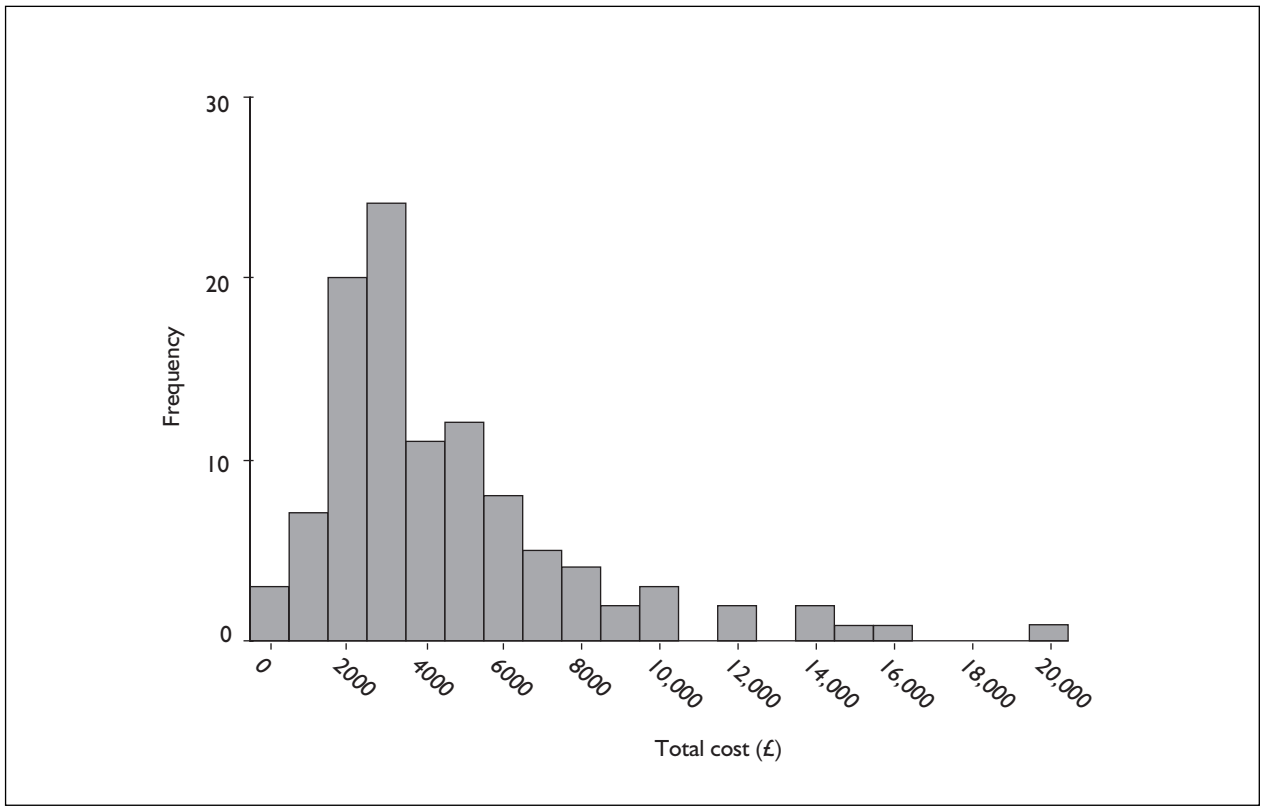

FIGURE 49 *Histogram of spread of total cost values for SEMS patients*

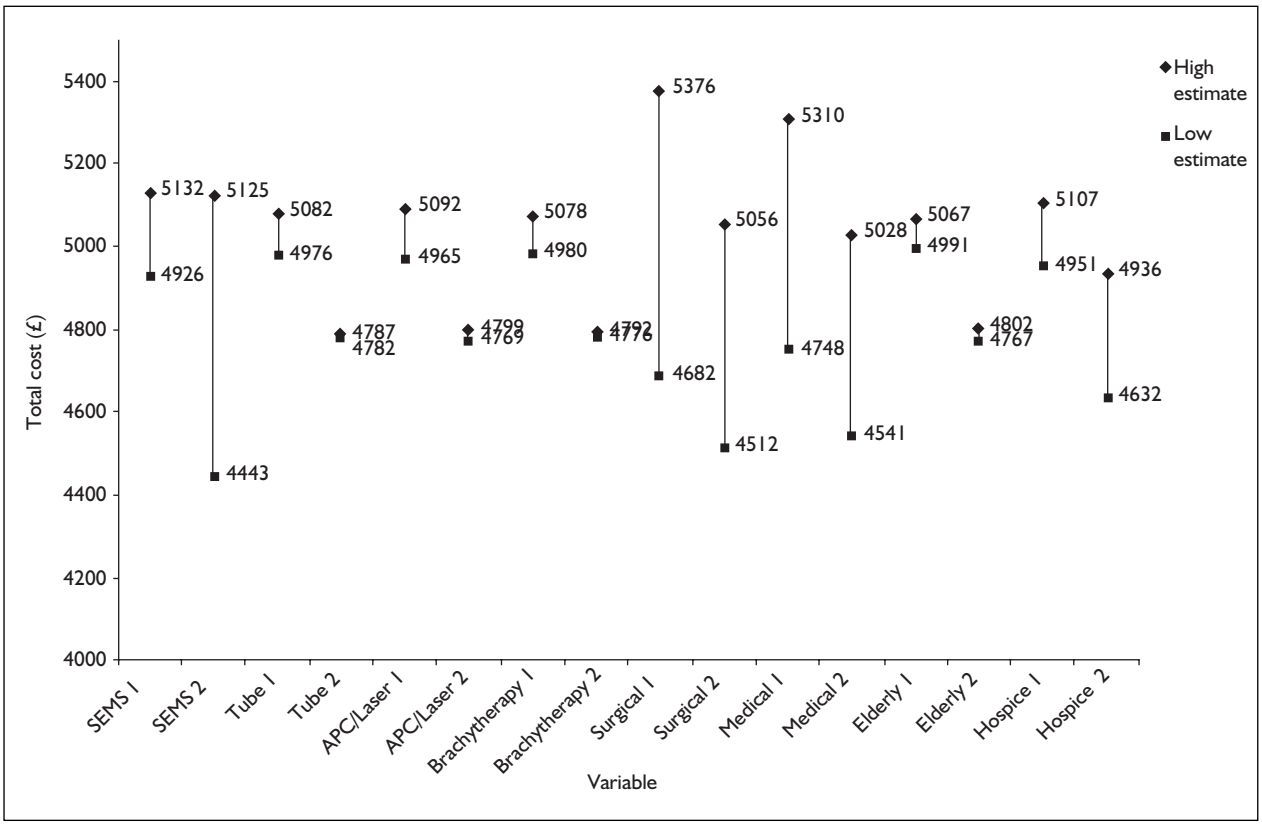

FIGURE 50 *Sensitivity analysis*

followed by 2 are the low and high estimates for the non-SEMS treatment arm for variation of the same parameter. Statistically, there were no significant differences between the treatment arms in the sensitivity analysis (*Table 95*).

Threshold analysis

Non-parametric bootstrapping was used to assess the effect of changes in the price of metal stents on cost differences. A sample of 1000 mean total cost observations was generated for the SEMS group for different purchase price values of the SEMS (£400–1200) and the generated costs were compared with a sample of 1000 mean total cost observations for the non-SEMS group. The resulting distributions were compared with computing the number of times that costs were lower in the SEMS group for the different price values and the frequencies plotted against the different SEMS price values to produce a cost acceptability curve (*Figure 51*). This demonstrates that at the baseline SEMS price of £1200, the probability of the total cost of SEMS treatment being cheaper than non-SEMS treatment is 56%. However, as the purchase price of SEMS treatment decreases, the probability that SEMS are ultimately cheaper increases, with a value of 98% when SEMS are priced at £400 (*Table 96*).

QALY analysis

To determine the QALY values for the treatment arms the EuroQol EQ-5D scores were first converted into a published tariff equivalent. An 'average' EQ-5D value was generated for each patient across all their assessments from randomisation to death or study closure. This value was used to generate the QALY values. There was no statistically significant difference in the average tariff-adjusted EQ-5D value between the study treatment arms (*Table 97*).

Generation of QALY values for the two main treatment arms is demonstrated on a simple boxplot (*Figure 52*), which also suggests little difference between the treatment arms. Although this was confirmed by statistical analysis, it must be noted that the mean QALY values for the patients in the non-SEMS group were 40% higher than those for the SEMS group (*Table 98*).

Cost-effectiveness

The difference in costs (for baseline cost values) and the difference in QALYs between the two treatment arms were then compared. *Figure 33* shows 1000 replications of cost differences (SEMS group minus non-SEMS groups) and QALY

TABLE 95 *Sensitivity analysis treatment arm comparison*

Cost variable	Variation of estimate	SEMS mean total cost ± SD	Non-SEMS mean total cost ± SD	Mann–Whitney *U* *p*-value
SEMS treatment	High	5132 ± 4439	5125 ± 3562	0.65
	Low	4926 ± 4285	4443 ± 3454	0.35
Rigid intubation	High	5082 ± 4357	4787 ± 3505	0.66
	Low	4976 ± 4362	4782 ± 3507	0.87
APC/laser therapy	High	5092 ± 4406	4799 ± 3539	0.68
	Low	4965 ± 4316	4769 ± 3475	0.84
Brachytherapy	High	5078 ± 4387	4792 ± 3524	0.71
	Low	4980 ± 4334	4776 ± 3489	0.85
Surgical ward stay	High	5376 ± 4812	5056 ±3798	0.73
	Low	4682 ± 3944	4512 ± 3260	0.83
Medical ward stay	High	5310 ± 4596	5028 ± 3704	0.74
	Low	4748 ± 4145	4541 ± 3350	0.82
Elderly care ward stay	High	5067 ± 4437	4802 ± 3523	0.76
	Low	4991 ± 4296	4767 ± 3492	0.77
Hospice care	High	5107 ± 4416	4936 ± 3716	0.80
	Low	4951 ± 4315	4632 ± 3326	0.74

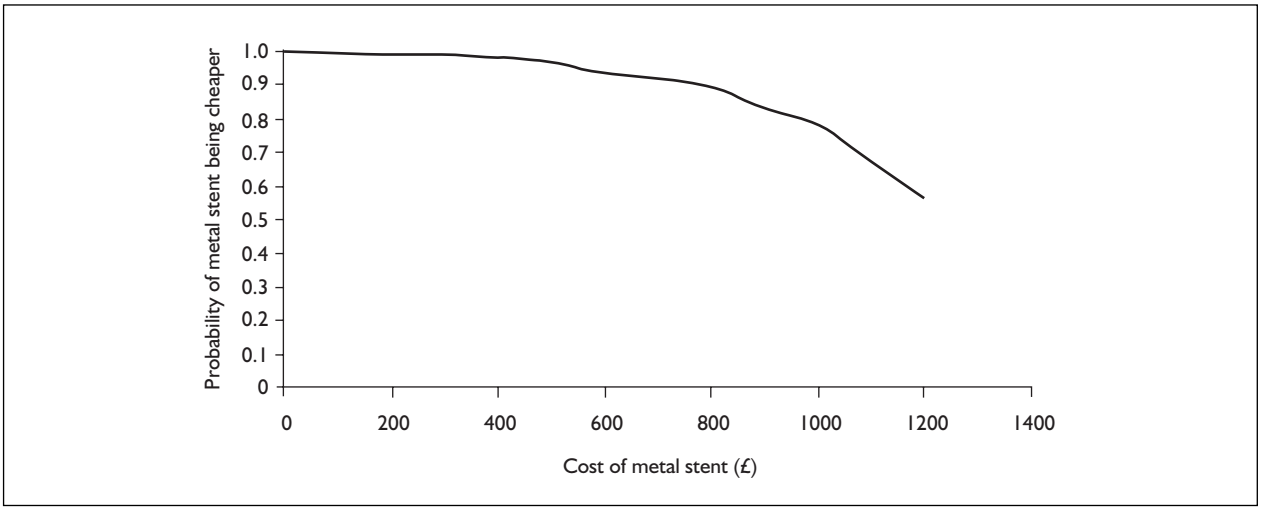

FIGURE 51 *Cost acceptability curve*

TABLE 96 *Cost acceptability data*

Purchase cost of SEMS (£)	Probability of total cost of care being cheaper
400	0.981
500	0.968
600	0.935
700	0.913
800	0.895
900	0.829
1000	0.786
1200	0.565

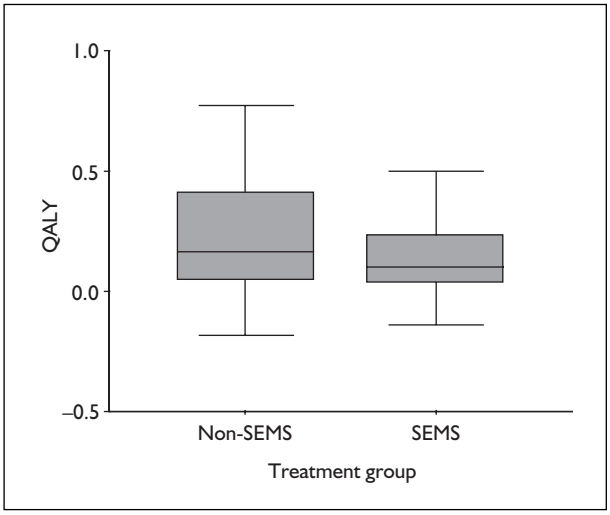

FIGURE 52 *Boxplot of mean QALY values for treatment arms*

TABLE 97 *Tariff-adjusted EQ-5D by treatment arm*

Treatment group	Assessment	Tariff-adjusted EQ-5D	Mann–Whitney *U* *p*-value
Non-SEMS	Baseline	0.56 ± 0.35	0.659
SEMS		0.56 ± 0.30	
Non-SEMS	Week 1	0.53 ± 0.35	0.042
SEMS		0.46 ± 0.32	
Non-SEMS	Week 6	0.49 ± 0.36	0.256
SEMS		0.45 ± 0.32	
Non-SEMS	Average	0.47 ± 0.29	0.290
SEMS		0.44 ± 0.25	

TABLE 98 *Comparison of QALYs*

QALYs	Mean QALY ± SD	*t*-Test *p*-value	Mann–Whitney *U* *p*-value	Log QALY *t*-test *p* value
Non-SEMS	0.25 ± 0.28	0.097	0.061	0.32
SEMS	0.18 ± 0.25			

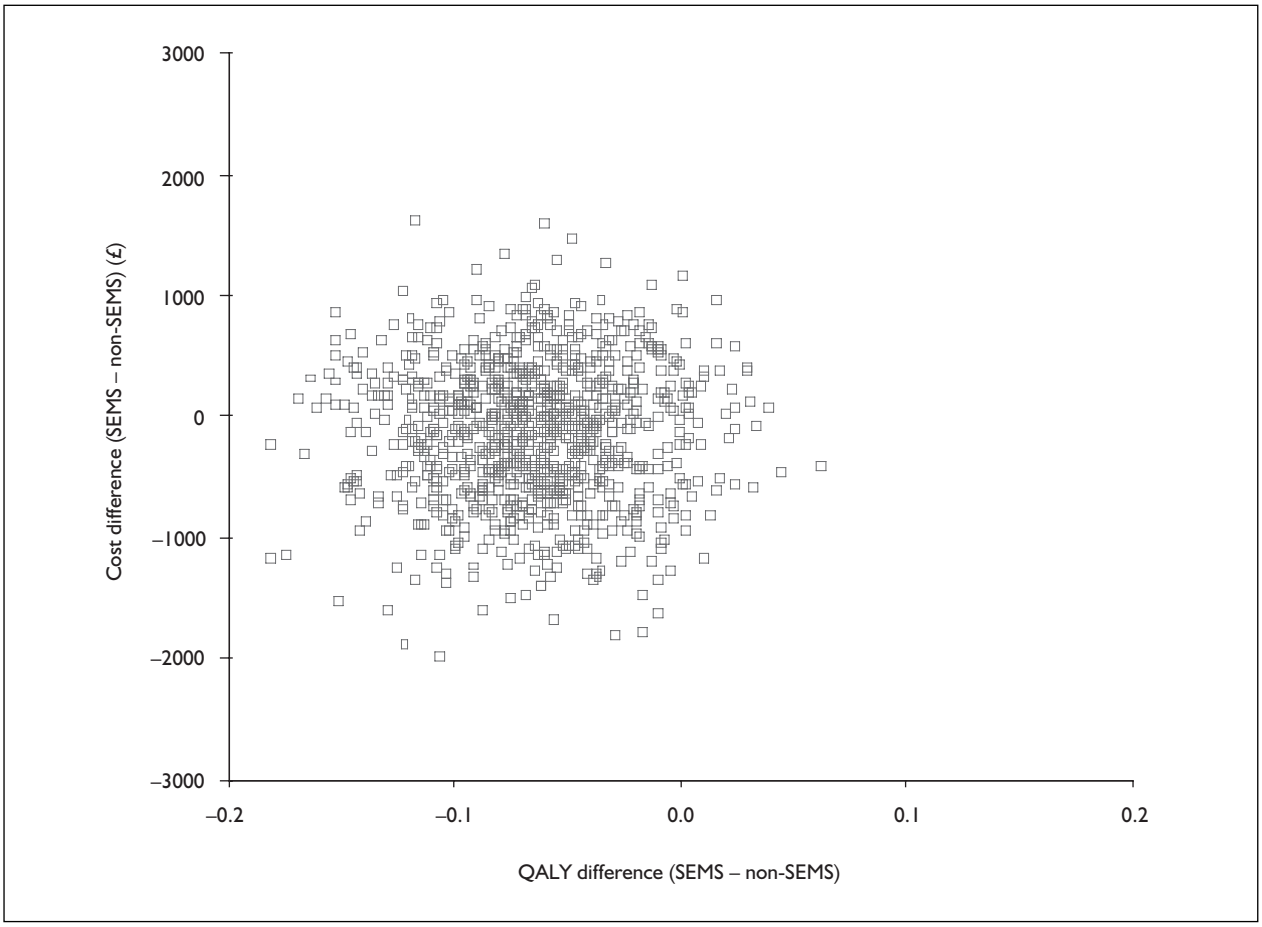

FIGURE 53 *Bootstrap plot of cost difference by QALY difference: SEMS versus non-SEMS*

TABLE 99 *Bootstrap data analysis*

Bootstrap variable	No. of replications	Observed mean total cost of QALY ± SE	95% CI		Correction
			Lower	Upper	
Non-SEMS total cost	1000	4792.91 ± 406.47	3995.27	5590.54	Normal
			4055.88	5626.23	Percentile
			4044.15	5595.55	Bias
SEMS total cost	1000	4648.72 ± 353.98	3954.09	5343.35	Normal
			3977.64	5350.15	Percentile
			4007.09	5379.53	Bias
Non-SEMS QALY	1000	0.25 ± 0.03	0.19	0.30	Normal
			0.19	0.30	Percentile
			0.19	0.30	Bias
SEMS QALY	1000	0.18 ± 0.03	0.13	0.23	Normal
			0.14	0.23	Percentile
			0.14	0.23	Bias

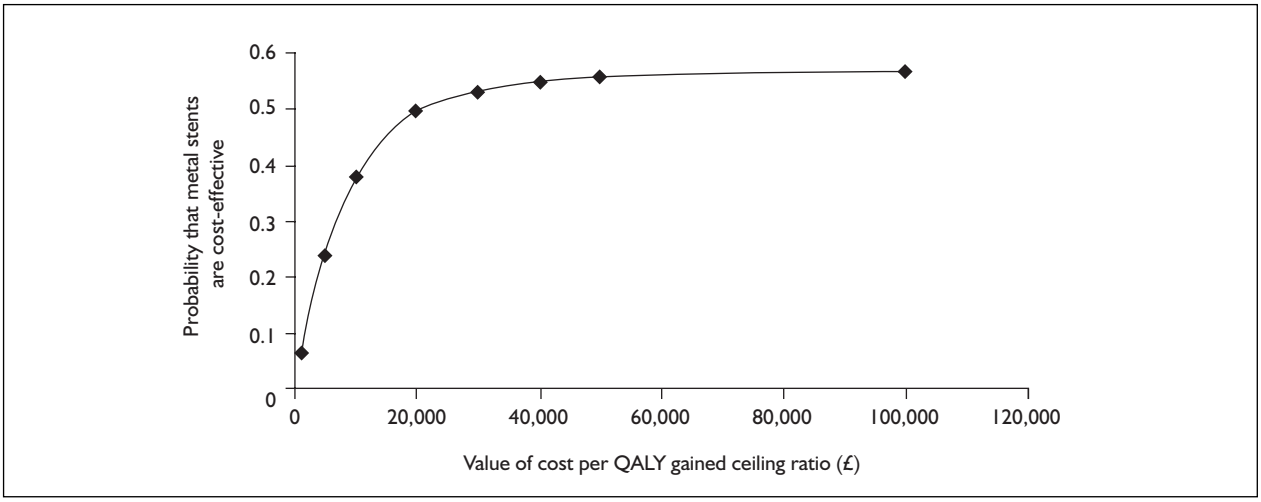

FIGURE 54 *Cost-effectiveness acceptability curve*

differences (SEMS group minus non-SEMS group). This plot suggests that patients in the non-SEMS group are more likely to have greater QALYs than SEMS treated patients, but that costs are almost equivalent between the groups. This was confirmed by the analysis (*Table 99*). A cost-effectiveness acceptability curve (*Figure 54*) was generated from these data, which demonstrates the probability of the SEMS becoming cost-effective for different predefined cost per QALY thresholds. *Figure 54* shows the frequency with which the cost-effectiveness of metal stents relative to non-stents fell below predefined cost-effectiveness thresholds. The message from this diagram is that metal stents are unlikely to be more cost-effective than non-metal stents within usual limits of acceptability. The main reason for this can be seen from *Figure 53*: as costs between the two groups were similar, the poorer survival associated with metal stents almost always led to lower QALYs and therefore less favourable cost-effectiveness estimates.

Chapter 4
Discussion

Population characteristics

Recruitment

The problems of conducting RCTs in palliative patient groups are well documented and this study was no exception, with poor recruitment throughout in relation to expected centre yields and overall targets. Initially, a delay in the appointment of local research nurses together with local political and logistical difficulties accounted for poor recruitment, but thereafter ambitious predictions of throughput and the more generic difficulties of entering palliative patients into a randomised treatment study became more apparent. Expected centre yields were not a true reflection of throughput. Although one centre reached 96% of expected recruitment, none of the remaining centres reached even 50% of their target, which was disappointing. Randomisation of palliative treatments was found to be difficult to apply, with the concerns of patients and referral sources adding to the problems of confronting quality of life issues in terminally ill people. In this regard, the enthusiasm of the medical staff and research nurses and their ability to explain the study clearly were essential, although there was no coercion, force or intimidation for patients to enter the study, as evidenced by the low withdrawal rate of 8% (n = 17), with only two patients (1%) withdrawing immediately after randomisation, having changed their mind about enrolment.

To improve recruitment a further centre was set up and a study time extension agreed for all centres. However, the total recruitment objective of 300 patients, as set by power calculations, was never achieved. Projection suggested that at least one further year would be required to achieve this target, but enthusiasm was waning in the centres and it seemed likely that recruitment would fall further, making this target difficult to reach. Furthermore, since new treatments are being developed, the results of the study could be out of date by the time of publication. As such, the trial was closed after 695 patients had been assessed for study entry, with 217 patients satisfying the entry criteria and 478 patients excluded. Of the excluded patients, 437 (91%) did not meet the study entry criteria, 293 of whom (67%) were suitable for potentially curative treatment. Only 27 of the assessed patients (4%) refused study entry, 33 (85%) of whom had predetermined treatment preferences, did not want to be part of a trial or refused all treatment. Excluded patients had equivalent gender matching to the study group, but were younger ($p < 0.0001$) than the study patients.

Patient and tumour demographics

The entry cohort of patients was representative of a typical UK palliative oesophageal cancer population with well-matched treatment arms to ensure accuracy of findings.[2] This has been a problem in previous research owing to the heterogeneous combination of elderly patients with early disease and young patients with aggressive distant spread.[33] There are no population studies of inoperable oesophageal cancer, but a 10-year review of practice was carried out in one of the larger study centres (Newcastle upon Tyne) before this trial.[302] From these data, the median age of palliated patients (n = 379) was 73 years (range 27–97), with a male to female ratio of 1.6:1 and a 50:50 split between ACA and SCC. The male to female ratio in this trial was 2:1, with a mean age at trial entry of 74.8 ± 9.0 years, comparable to the Newcastle review, but the ratio of ACA to SCC is now 60:40, reflecting recent changes in epidemiology.[303] All study groups were matched for gender and histological subtypes; however, the mean age of the SEMS group was 3 years less than the non-SEMS group. This could have an effect on survival and quality of life, as younger patients may be subject to a different disease natural history and tend to assume a 'life at any cost' mentality. However, 3 years is not a great difference and is unlikely to have an effect unless accompanied by a difference in tumour stage between groups. Analysis confirmed that there was no difference in stage distribution between the groups, although significantly more patients randomised to the non-SEMS arm were classified as unfit for surgery ($p = 0.048$). As a result, many of these patients did not undergo full staging, as trusts were unwilling to utilise overburdened CT and EUS facilities in patients deemed palliative by virtue of their physical fitness. As such, in addition to the age difference between treatment arms, there were more

TABLE 100 *Comparison of primary causes of inoperability*

Primary cause of inoperability	Newcastle study[302]	Current study	Roseveare *et al.*, 1998[245]
Metastatic spread	83 (22%)	52 (27%)	6 (19%)
Locally advanced disease	167 (44%)	53 (27%)	4 (13%)
Poor fitness/no documented spread	129 (34%)	97 (46%)	21 (68%)
$\chi^2 = 6.38$, 2 df, $p = 0.041$.			

understaged patients in the non-SEMS study arm. These patients could have had less advanced disease, with important implications for survival.

Overall, a significantly greater proportion of patients was classified as unfit in this study and significantly fewer had locally advanced disease in comparison to the Newcastle review (*Table 100*). This raises the possibility of selection bias, with clinicians being more likely to enter unfit palliative patients into this trial than those with locally unresectable disease, as many clinicians believe that radiotherapy has advantages in the palliation of local disease because of the tumour destruction effect, despite a lack of published evidence. Most previous studies have not presented staging data, so comparison is not possible, except with the study by Roseveare and colleagues, in which the greatest proportion of patients had no documented spread. Assuming that staging was less likely to be carried out in unfit patients, as seen in the present work, this group would correlate with unfit patients, which supports the hypothesis of a clinician-determined selection bias.[245]

Outcomes

Dysphagia

Dysphagia relief is the primary outcome measure of this study and all groups were associated with significant relief of dysphagia after treatment. The effect of treatment was maximal at 6 weeks and was independent of baseline dysphagia status. By the week 6 assessment, 67% of patients had improved swallowing, with no differences between the SEMS and non-SEMS arms of the study. However, subgroup analysis demonstrated a difference between the treatment subgroups, with patients receiving rigid tubes having a worse mean dysphagia score at 6 weeks than patients in the other groups (rigid tube group 1.42 ± 1.00 versus collective other treatments 0.92 ± 1.04, where a lower score equates to better swallowing). Dysphagia scores deteriorated in all groups following the week 6 assessment, which suggests that the week 6 value is most accurate for treatment comparisons.

Differences between palliative treatments in the relief of dysphagia are small and hard to quantify, so comparative research is scarce and tends to concentrate on differences in treatment-associated morbidity. Most studies are comparisons of SEMS and rigid intubation, and of the six randomised comparisons, none demonstrated better dysphagia relief with tubes and two found that SEMS were more effective.[201,245] Laser treatment was also associated with a better quality of swallowing in comparison to rigid intubation in one randomised study.[256] Non-randomised research tends to support the same conclusion, that rigid tubes do not provide as good functional success as other palliative modalities. Only one randomised study has compared the functional effects of non-rigid tube treatments. This compared laser to SEMS and reported better functional success with SEMS.[251] However, most non-randomised, observational research has demonstrated broadly similar dysphagia relief with non-rigid tube therapies.[252]

Most comparisons use the standard five-point dysphagia scale, which is useful for comparisons but clinically irrelevant as mean scores fall between the point values. In this study, at 6 weeks non-rigid tube patients had a mean dysphagia score of 0.92 compared with 1.42 for the rigid tube group, neither value correlating to a swallowing grade despite being significantly different, with a better quality of swallowing for the lower value group. Median scores are more clinically relevant, but differences in swallowing between groups vanished when these were analysed. It therefore becomes necessary to analyse nutritional data and quality of life to see whether the mean dysphagia score differences are relevant in clinical terms. When these analyses were performed the differences in swallowed diet were not found to be reflected in nutritional status or quality of life; thus, patients receiving rigid tubes may have a worse mean dysphagia score at 6 weeks but do not lose weight

or grip strength more rapidly than the other groups or have worse quality of life, nor are they worse symptomatically or have more trouble enjoying food. This is in contrast to one randomised study, which found greater food enjoyment in SEMS patients compared with rigid intubation.[245] As such, the clinical relevance of the observed difference in dysphagia grade is difficult to interpret, but the fact remains that the current trial has demonstrated a significantly worse mean dysphagia score in patients receiving rigid intubation than the other treatments.

The median dysphagia values for treatment subgroups demonstrate that all treatments are associated with improved swallowing to a near-normal diet. However, those receiving an 18-mm SEMS achieved the best median dysphagia score, equating to eating a normal diet. The 24-mm SEMS was introduced primarily to reduce stent migration, a significant problem with early model SEMS, but the larger cross-sectional area was also expected to improve the quality of the swallowed diet. Only one previous study has compared two sizes of the same SEMS; this was also based on the Gianturco Z-stent. Based on complication rates this study concluded that the larger SEMS was a significant improvement on the smaller model; however, the study was non-randomised and failed to include comparative dysphagia data.[217] The results of the current trial indicate that in terms of relief of dysphagia the 24-mm SEMS shows no improvement over its 18-mm counterpart.

Only six patients received BICAP and ETN as primary treatments. All experienced absolute dysphagia following treatment, five required urgent retreatment with a stent and the remaining patient deteriorated rapidly and died. A previous study noted that one-third of the patients referred for palliation are not suitable for BICAP and, despite some studies of ETN demonstrating better results when used for specific tumour morphological types (e.g. polypoid, exophytic lesions), the degree of necrosis is unpredictable.[76,86–88] Although based on extremely low patient numbers, the results in comparison to the other therapies reflect that these treatments should only be used as secondary therapy for overgrowth, ingrowth and recurrent dysphagia, where they have been shown to play an important and useful role, and not as primary therapy except in exceptional circumstances.

Nutrition

Only one randomised study has included nutritional parameters in a comparison of treatments. Roseveare and colleagues demonstrated that patients treated with SEMS lost less weight than rigid tube patients in the week following treatment.[245] Thereafter, there were no significant differences between groups, but there was a trend towards greater weight loss in the tube group. The observed difference was felt to be due to a higher calorific intake in SEMS patients because of improved dysphagia relief. However, the dysphagia characteristics of the groups were analysed as a median of all assessments after insertion, not as point estimates, which is an inaccurate method of comparison as it is influenced by other factors such as survival and baseline dysphagia status. Furthermore, first week weight loss in dieting individuals is due to water dehydration, not calorific intake, and as a result is essentially meaningless. Although equal and active encouragement was given to optimise oral intake after discharge, and differences in weight loss after the first week may have been due to altered dietary intake, many other confounding factors such as steroid use were not studied and bias may have resulted from neither staff nor patients being blinded to the treatments used. In the current study, a variety of nutritional parameters was collected and analysed, including weight, grip strength and serum protein levels. Dietary advice was identical and standardised. Staff and patients were blinded when a stent was used, but this was clearly not possible for patients in the non-stent subgroup. All nutritional markers deteriorated in the participants following diagnosis, with no differences between the treatment groups or study arms despite effective dysphagia relief. This suggests that restoration of normal nutritional intake is more complex than the effective relief of oesophageal obstruction. Persistent dysphagia has been noted following tumour debulking despite the clearance of luminal disease, possibly as a result of motility disturbances. In addition, dysphagic patients take time to regain confidence in swallowing after effective treatment owing to fears about regurgitation and choking; this has been termed "tumour anorexia".[55–57,245] However, these factors do not account for the continuing deterioration in nutrition in all patients, and it is likely that other factors such as progression of disease, cancer cachexia and mental attitude are important variables in nutritional status.

Of relevance to this present study is that differences in dysphagia were not reflected in changes in anthropomorphic or biochemical nutritional parameters. This suggests that the differences in dysphagia grade between treatments were too small to be of clinical importance, or that

any deficiencies were concealed by calorific intake changes initiated by the patients or paramedical staff to maintain weight.

Quality of life

Researchers have demonstrated improved quality of life in patients with inoperable oesophageal cancer following relief of dysphagia, but few have used the concept in comparative evaluations of palliative therapies.[3,41,245,285–287] Barr and colleagues found no difference in the quality of life of patients treated by laser therapy alone or followed by intubation, despite more complications and a higher recurrence of dysphagia in the intubated group.[73] Similarly, Roseveare and colleagues demonstrated no difference in quality of life in SEMS and rigid tube-treated patients, despite better nutrition and swallowing in the SEMS group.[245] These researchers expected dysphagia to be a major influence on quality of life, whereas Blazeby found that dysphagia only accounts for 15–20% of variance in quality of life.[5] This is corroborated by the findings of this study, with quality of life deteriorating in all patients after diagnosis despite effective treatment. This suggests that other factors have more impact on quality of life than dysphagia grade alone.

Three of the four scales demonstrated a difference in quality of life scores between the study arms 1 week after treatment. Only the proxy assessed, Karnofsky scale showed no difference at this point. The difference appears to be due to a significant drop in quality of life following SEMS treatment which does not occur in the non-SEMS patients, but by 6 weeks the quality of life scores for the two arms approximate. It appears that SEMS patients experience an adverse event that affects quality of life immediately after treatment, but thereafter has less effect. The difference in the QL index and EuroQol EQ-5D scores suggests that this effect may be a patient-centred phenomenon. These instruments are almost identical, yet EQ-5D scores were consistently lower than the QL index values. This may be due to the EQ-5D tariff values being based on preferences, whereas the QL index assumes equal weighting for different health impacts, or because EQ-5D is a self-completed questionnaire, whereas the QL index is proxy assessed which, in turn, implies that self-completion was more critical or proxy assessment was more optimistic. This may also explain the limited findings of the Karnofsky questionnaire. Barr and colleagues demonstrated the same effect with proxy and self-completed quality of life assessments.[73] This suggests that the lower quality of life scores for SEMS-treated patients may be secondary to a patient-experienced effect of which the clinician is not even aware. This hypothesis is clarified following detailed analysis of the EORTC quality of life data.

The QLQ C-30 functioning scale values deteriorated over the assessment period. This was most marked in the physical and role functioning scales, with patients finding it harder to perform activities of daily living as the illness progressed. In contrast, social functioning and emotional status were relatively well preserved. The values from these scales did not vary significantly between the treatments, other than cognitive function, which differed between arms at the week 1 assessment, with SEMS patients having lower scores at this time-point; that is, patients treated with a metal stent reported more difficulty than non-SEMS patients in concentrating and remembering things a week after treatment. This difference was not apparent at the 6-week assessment, which further substantiates the hypothesis of an adverse phenomenon affecting SEMS patients immediately after treatment. Analysis of the EORTC symptom scales showed that swallowing improved after treatment, with patients eating more varied foodstuffs in a less troublesome and more enjoyable manner, and no differences between study groups in this regard. However, reported pain scores differed significantly. Two pain scales were used, with comparable findings. The OES24 pain symptom score reported considerably more pain after treatment in stent patients than in the non-stent patients, who had unchanged pain scores across time-points. This was statistically significant at week 1. By the week 6 assessment pain scores for rigid tube and 18-mm SEMS patients returned to pretreatment levels; however, patients treated with 24-mm SEMS continued to report higher pain levels.

Since all other quality of life domains were comparable between treatment subgroups and study arms, it is likely that the observed differences in quality of life after treatment are due to differences in pain. Patients treated by stents, especially metal stents, experienced higher pain levels, and this may explain the difference in cognitive functioning as patients would find it harder to concentrate if experiencing pain. Pain is commonly reported after stenting of the oesophagus, but is unpredictable. As a general rule, the larger the SEMS diameter or the greater the radial force exerted, the greater the associated pain.[189,190] Observational studies have reported severe pain in 10–60% of patients after placement of a SEMS.[179,187,188,208] This affects analgesic

requirements, with potentially important implications. Golder and colleagues monitored daily opioid analgesic requirements in 52 patients palliated with SEMS and found that 26 patients (50%) required opioid analgesia within 48 hours of the procedure (median dose: 80 mg morphine/day).[207] This could decrease conscious levels and increase the risk of aspiration pneumonia, especially if the SEMS straddles the oesophagogastric junction.[173,181,197] The effect of post-treatment pain on quality of life has not been reported previously and has significant implications for treatment with a SEMS.

Health state utilities substudy

This substudy compared the utility scores obtained using chained TTO and SG methods in a sample of patients who had received curative oesophageal cancer treatment, but the results provided information about a palliative population. There is mixed evidence with regard to how personal experience of particular health states or treatment can affect valuation. Boyd and colleagues[297] and Sackett and Torrance[298] suggest that impaired health states are valued more positively when experienced than when hypothetical but in contrast, de Haes and Stiggelbout[295] found the opposite to be true and Llewellyn–Thomas and colleagues[304] reported that cancer patients' preferences for a hypothetical state were similar to the same patients' preferences when they entered that health state. In this substudy, the selected participants had experienced one or more of the symptoms described in the health states and all had previously made similar treatment choices so that the scenarios were less hypothetical than an inexperienced population. However, their previous choices had been related to curative rather than palliative treatments, so it is an assumption that these 'lucky escape' cured patients' valuations of health states approximate to those of an 'unlucky' palliative population. Additional research would be required to show whether prospective candidates for palliative therapies, or the general public, would value these states differently. As such, concrete conclusions are hard to justify, but nevertheless this patient group comes as close to a palliative population as can be ethically drawn and still carry the label of only 'potential cure'. The patients and their clinicians are well aware of this, and of 112 potential participants, 43 were excluded by the clinical team owing to concern regarding potential recurrent disease, and of the remaining 15 who did not complete the data collection, five refused and ten were too upset to continue once they understood the nature of the study.

As to the study findings, there was a high completion rate and a high number of participants who ranked consistently for both methods. These results suggest that both valuation methods are acceptable to use within this particular patient group. There were significant differences between states within both TTO and SG groups, which provides evidence for the improved sensitivity of the chained method, as shown by other studies.[305] Most strikingly, patients expressed strong individual treatment preferences specifically concerning radiotherapy treatment, with patients showing distinct preferences for or against radiotherapy depending on previous experiences and those of friends, family and acquaintances. These individual preferences cancelled out when aggregated, but were strongly held beliefs that should not be disregarded when selecting a palliative treatment.

Delay, admissions and hospitalisation

After the exclusion of patients who were knowingly subjected to treatment delay, there was a greater treatment delay for patients receiving non-stent therapies. Patients randomised to a stent therapy waited a week for treatment, whereas patients in the conventional care group waited 2 weeks for treatment. Some delay is acceptable unless absolute dysphagia is present and, for the purpose of this study, centres were obliged to offer a period of reflection for potential patients of at least 48 hours so that they did not feel pressurised into consenting to enrolment. However, the observed delay for non-stent treatments was specifically due to radiotherapy. Patients had to wait for an average of 20 days before treatment planning and longer for actual treatment, whereas patients receiving the non-radiotherapy, non-stent treatment waited for only 9 days, which was comparable to stent therapies. There is no apparent clinical reason for this radiotherapy delay and it appears anecdotally to be due to overburdened systems. This has significant resource implications, since during this lag time, dysphagia may become absolute and require hospital admission as well as adversely affecting quality of life owing to the psychological status of the 'untreated' terminally ill. Analysis did not confirm this, demonstrating unaffected quality of life, but the non-stent subgroup did require significantly more pretreatment endoscopic dilatations ($p < 0.001$), with associated hospital attendance and risk of perforation. These logistical difficulties of access to palliative treatment have not been addressed in any research, but it is clear that problems exist even within specialised centres.

Although there is currently no evidence base as to what constitutes an ideal treatment, common sense suggests certain parameters, such as achievement of dysphagia relief in the minimum number of therapeutic sessions. Stenting is designed to be a one-off treatment, requiring only one admission and procedure to relieve dysphagia permanently. In this study, each stent patient had a median of two admissions (range 1–23), one for treatment and one subsequently for complications, further palliation or terminal care. In contrast, non-stent therapies were associated with a median of five admissions per patient (range 1–16), significantly higher even after adjustment for length of life. This was as a result of additional retreatments, both scheduled as a function of the nature of treatment (e.g. EBRT fractions) and unscheduled owing to extra dilatations during the wait for definitive treatment. This did not increase total hospital stay when corrected for length of life or affect quality of life, but the increased hospital attendance is demanding for elderly patients. In fact, one of the specific concerns raised by the health state utilities' unstructured interviews with patients was of repeated transportation to hospital.

Inpatient hospital stay consumes greater resources than many other health service interventions and as such is of great importance in this cost-effectiveness study. Hospital stay was divided into initial and total stays to reflect the occurrence of initial complications and overall hospital attendance. The median initial hospital stay was 3 days (range <1 to 71 days), with a shorter initial stay for patients in the non-stent subgroup ($p < 0.001$). This was expected and reflects the need for education of stented patients to ensure optimal oral intake before discharge, rather than the incidence of early complications, which were uncommon in all groups. The length of initial hospital stay for rigid tube patients was shorter than has been reported in previous research. Two randomised, controlled clinical trials have reported the length of initial stay after treatment by rigid intubation and SEMS; the mean time to discharge or death after intubation was between 9 and 10 days, but was only 4 days for SEMS in both studies.[180,145] In the current study, rigid intubation was associated with exactly the same length of initial stay as SEMS treatment. This may reflect the less aggressive insertion technique used and thus the lower risk of early complications. The technique was the same as that used in a previous Newcastle study that also reported a short postprocedural stay (median 5 days) for rigid intubation, again comparable to that of SEMS and to this study.[40]

There was no difference in total hospital stay between the treatment arms, with a median of 14 days (range 1–103) for all patients. Patients in the non-stent and 18-mm SEMS subgroups appeared to be subject to longer stays, thereby implying that they had more problems; however, total hospital stay alone is not evidence of the effectiveness of palliation or the complication rate: complications can increase total hospital stay, but so can survival; a patient dying as a result of treatment will have a short stay, but a patient surviving for a long time will have repeated admissions for minor complications and a lengthy total stay. As such, a long hospital stay may actually reflect better palliation rather than more complications. Analysis confirmed this supposition, with a significant association between length of stay and length of life ($p < 0.001$). To circumvent these factors total length of hospital stay was corrected for length of life to give 'total length of stay per week of life'. Previously identified differences between groups were no longer present. Non-stent treatments are known to require significant hospital attendance, and Barr and colleagues reported a mean total hospital stay of 13.7 days for laser therapy, which is directly comparable to this study.[73] However, stent therapies are generally associated with short hospital stays, especially for SEMS. Knyrim and colleagues reported a longer mean total stay for rigid tube patients compared with SEMS patients (12.5 versus 5.4 days, respectively, $p = 0.005$).[306] A similar but non-significant trend was noted by Roseveare and colleagues (median total stay 12 days for rigid intubation versus 8 days for SEMS, $p = 0.5$).[245] These results may again be a function of differences in insertion techniques and associated morbidity, as O'Hanlon and colleagues, using a less aggressive insertion technique of rigid intubation, reported a mean total stay of 8.2 days, which is closer to that seen with SEMS treatment.[40] However, a fair proportion of total stay is due to hospice care and repeated hospital attendance, factors often disregarded by other studies.

Mortality and complications

Early complications are common with all palliative treatments and this study was no exception, with 37% of patients ($n = 78$) affected. However, in contrast to previous research there were few differences in morbidity between the treatment arms or groups. Only total dysphagia immediately after treatment and late migration were significantly different between the groups. Total dysphagia occurred almost exclusively in patients treated by BICAP or ETN and late migration was more common with rigid tubes.

Aspiration was uncommon after treatment (2%) and only occurred when a stent was placed across the oesophagogastric junction. However, since 91 patients were treated in this manner, aspiration occurred in one in 20 oesophagogastric junction stent placements (5.5%) and all cases were fatal. This is comparable to published data, which place the risk of aspiration between 3 and 9%.[40,146,151,173,181,197] Researchers have suggested that, although uncommon, aspiration probably accounts for many unexplained early deaths, especially in the presence of opiate analgesia. Seven patients deteriorated after treatment to death while still in hospital, which could have been due to unknown aspiration. In addition, 35 patients (16.8%) had severe, disabling pain requiring hospitalisation and opiates after treatment, 28 of whom had primary stent treatment. All of these patients had the potential for aspiration. Nevertheless, this was uncommon as a late pathology and only occurred in SEMS-treated patients. The use of proton-pump inhibitors probably limited oesophagitis-related morbidity.

Perforation of the oesophagus was not as common as expected, with only three procedure-related perforations occurring (1.4%) and only one patient dying as a result. Each occurred with different therapies: one as a result of dilatation before brachytherapy, one after rigid intubation and one after the placement of a 24-mm SEMS. Two further perforations occurred as late events, but were felt to be due to spontaneous tumour perforation rather than a result of treatment. Perforation after rigid intubation has been a major drawback of the treatment, with the literature suggesting that it occurs in up to 13% of procedures, although most are small and conservative management is successful in the majority.[4,40,143,151,154] The perforation rate for intubation in this study was less than 2%, a striking improvement, which is probably the result of using a less aggressive insertion technique. This was based on the technique used in a contemporary study where only one procedure-related perforation occurred in 70 intubated patients (1.4%).[40] Most early series report no SEMS-related perforations, although they can occur in up to 7% of procedures.[173,181,188,189,193,197,203,206,209–211] Only one metal-stent related perforation was seen in this study, supporting the low but nevertheless significant perforation rate. No perforations occurred in laser or APC patients despite more pretreatment dilatations, but one occurred fatally in a patient dilated before brachytherapy. A previous study demonstrated that if clinicians are aware of potential pitfalls of treatment this can reduce mortality.[162] Given the nature of prospective data collection in this study, there is no doubt that the trial collaborators used caution in performing all treatments, and the overall low perforation rate is reassuring and suggests that a greater awareness of potential risks and careful patient selection can reduce morbidity and mortality.

Migration and obstruction are particular to oesophageal stenting therapies, often requiring retreatment. Tumour ingrowth through metal mesh designs was a major problem when SEMS were first introduced. To reduce the incidence covered SEMS were launched, which in turn increased migration rates. Subsequent designs have incorporated features to reduce migration, including barbs, uncovered sections and the introduction of the larger diameter SEMS. The early migration rate in this study was 7%, occurring equally between all stent therapies immediately after placement or within the first two weeks (n = 15). This is comparable to previously published research. All stents migrated distally and although none required removal, migration necessitated repositioning or replacement. The stent diameter made no difference, with the same early migration rate observed for both 18-mm and 24-mm SEMS. Late migration was significantly more frequent with rigid intubation (20%) than with SEMS (3%) and was also more common when a secondary stent therapy was used after the failure of a primary non-stent treatment. Ingrowth did not occur since all stents were covered, but overgrowth occurred in 6% and was readily treated by ablative techniques or further stent placement. There was no difference between the stent treatments in rates of overgrowth. Food bolus obstruction was significantly higher after rigid intubation (χ^2 = 9.28, 3 df, p = 0.026) than SEMS therapies, lending weight to the argument that the cross-sectional area of the available lumen is important in the quality of the swallowed dietary intake.

Bleeding rarely requires more than supportive treatment with blood transfusion. This occurred in nine patients (4%) immediately after treatment and 37 of patients (9%) later in their clinical course. Although there were no differences between study arms, problematic bleeding appeared to be more common in rigid tube and 18-mm SEMS-treated patients. This cannot be explained.

Although fibrous cicatrisation is said to be common after oesophageal radiotherapy, only one

of 26 patients (4%) treated by primary radiotherapy developed a post-treatment stricture requiring dilatation. This patient had received both EBRT and a brachytherapy boost, supporting the argument that this is a dose-related phenomenon that can be avoided.[104,105]

As a consequence of the comparable morbidity there were no differences in in-hospital or 30-day mortality between the treatment arms or groups; 14 patients (44%) had an unexplainable deterioration in their physical condition following treatment to death, with no specific cause found. Some of these patients may well have had concealed haemorrhage or unrecognised aspiration, since these were the most common recognised causes of death and occurred equally between treatment groups.

Technical success was high for all treatments at 98.6% with no differences between groups, but a significantly greater number of patients in the non-stent subgroup required more than one treatment course to achieve effective and lasting palliation of dysphagia ($\chi^2 = 41.06$, 3 df, $p < 0.001$). Only 13% of non-stent patients were palliated by one treatment course, in comparison to the stent therapies which all achieved similar success with 60–70% of patients successfully palliated with one therapeutic session.

Another problem with the non-stent therapies is the delay to treatment and, as such, 15% of these patients required an unscheduled, pretreatment dilatation for temporary dysphagia relief, which was not necessary for any of the SEMS patients ($p < 0.001$). Post-treatment dilatations were also more common in non-stent patients ($\chi^2 = 86.19$, 3 df, $p < 0.001$), which is not surprising given the need for further definitive palliative treatment. Rigid intubation was associated with a significantly greater number of post-treatment endoscopies ($\chi^2 = 35.48$, 1 df, $p < 0.001$) directly as a result of the higher observed rates of food bolus obstruction and late migration with the rigid tubes.

Survival

Research to date has not conclusively demonstrated any significant survival advantage between the various modalities of palliative therapy. Two previous non-randomised studies demonstrated a survival advantage for the additional use of palliative radiotherapy and chemoradiotherapy, but both were subject to selection bias and randomised studies have failed to replicate this.[163–166,229] Survival is important in palliative patients, but more as a 'non-hastening' of death as opposed to pure survival at any cost, and any potential advantage must be weighed against the costs of increased morbidity, protracted hospital stay or the need for repeated hospital attendance.[91] A recent randomised study by Dallal and colleagues comparing thermal ablative palliation with SEMS reported significantly longer survival in patients who underwent ablative therapies; 125 days (range 17–546) versus 68 days (range 8–602), respectively ($p < 0.05$), with no explanation for this finding.[307] Nicholson and colleagues also reported worse survival for SEMS-palliated patients compared with a variety of other therapies including rigid tubes and radiotherapy in a retrospective, non-randomised study, although this was not significant.[246] As such, survival was carefully monitored and recorded in this present study, but was not a primary outcome measure.

This study demonstrated a trend towards better survival with non-SEMS treatments. Further analysis was justified and regression modelling confirmed that the benefit was specifically due to patients in the non-stent treatment subgroup and was significant ($p = 0.03$). This difference is in the order of 30 days, a major effect in a terminally ill patient with a mean survival of only 13–19 weeks. Many patients in this group received radiotherapy; however, further analysis failed to demonstrate a difference in survival between those who received radiotherapy and those who received other forms of non-stent care. Unfortunately, there were discrepancies in the matching of the patient groups. The SEMS patients were on average 3 years younger than the non-SEMS patients, which may have an effect on the natural history of disease, and although there were no differences in tumour length or apparent stage of disease between the treatment groups, there were significantly more non-SEMS patients classified as unfit for surgery ($p = 0.048$). Since many of these unfit patients had not undergone the full staging protocol it is not known whether they had less advanced disease, with implications for the survival benefits observed.

The effect was small and was not a primary outcome for this study; nevertheless, a significant difference in survival was demonstrated and despite repeated hospital attendances for retreatment these patients maintained their quality of life so that the extra month's survival was worth this inconvenience. These results suggest that either non-stenting improves survival or stenting worsens it, so that the survival effect

may be greater given that there was a significant delay in commencing non-stent treatment. This effect could simply be as a result of improved clinical contact, since the non-stent treatments require regular hospital attendances, or may be due to detrimental biological effects of stenting, such as local tissue trauma. This is an area that requires further investigation and research.

Cost and cost-effectiveness

The modalities currently available in the UK for palliation differ considerably in purchasing and running costs. However, these costs could be exceeded by the costs of the resources consumed by reinterventions for complications of the treatment or recurrence of symptoms. As such, the high purchasing cost of SEMS could be offset if associated with a reduction in reintervention costs. In this regard, research to date has proved inconclusive. Two RCTs support the hypothesis,[245,306] but flaws in one study's design biased the results in favour of the SEMS treatment by increasing the morbidity associated with rigid intubation,[306] and the cost analysis of the other study was based on a comparison of early complications and initial stay, and did not take late reinterventions into account.[245] A further, more recent, randomised study with similar findings suggested that the initial high purchase cost was not offset by a lower reintervention rate, but far exceeded by the costs of inpatient stay after 1 month, and two non-randomised studies have not shown any significant difference between total costs for SEMS and rigid tubes.[180,245,246,249,267] The problem with all previous studies is the focus on initial 'trust' costs, with overall costs to the health service disregarded and no emphasis placed on length of survival or quality of life. In general, patients who live longer cost more as they require more reinterventions, so that the cheapest treatment could simply be the one with the highest early mortality.

In this study the costs were broken down into initial, interventional, hospital stay and total costs. Total costs from randomisation to death or study closure amounted to approximately £5000 per patient, with no difference between the study treatment arms. However, initial and interventional costs were significantly higher in SEMS patients as a result of the higher purchasing price of SEMS, which suggests that later costs may have been lower than the other therapies to make up for the overspend. This is not the case. Hospital stay costs far outweigh interventional costs, so that by far the majority of the total cost is made up from inpatient stay. As the total length of hospital stay for all patient groups was the same, this conceals the differences in the initial purchasing costs when the total cost of treatment is calculated. The sensitivity analysis confirms this, with the eight highest contributing variables being the four palliative treatment costs and the four most frequently utilised inpatient beds (including hospice care). The plot of the upper and lower mean total cost estimates for both groups in the sensitivity analysis initially suggests that the total costs for the non-SEMS group are lower; however, despite the apparent differences observed the scale of this graph is small and the confidence intervals for these point values (not demonstrated) were wide. Statistically, there are no significant differences between the treatment arms in the sensitivity analysis. SEMS are likely to reduce in price as manufacturing processes increase in efficiency, so non-parametric bootstrapping was used to assess the possible effect of changes in the price of SEMS on cost differences. The resulting distributions allowed the production of a cost acceptability curve, which demonstrated that at the current insertion SEMS price of £1200, the probability that the total cost of SEMS treatment is cheaper than non-SEMS treatment is 56%. However, as the purchase price is reduced, the probability that SEMS are cheaper increases, reaching a value of 98% when SEMS are priced at £400.

QALY values between the treatment arms approach statistical significance ($p = 0.061$). Given that the tariff-adjusted mean EuroQol scores for the two treatment arms are equivalent ($p = 0.290$), this implies that the effect being seen may predominantly be due to differences in the survival data, with the mean QALY values for non-SEMS-treated patients appearing to be higher than those of the SEMS group. This is consistent with the survival data and analysis. Despite the borderline statistical values obtained there are two important clinical features of the results: first, how low the QALYs are for all patients in the study – these values reflect that patients consider a year with their quality of life to be equivalent to only one-fifth of a year of normal health; and second, that the mean QALY value associated with the non-SEMS treatment group is 40% higher than that of the SEMS patients. This was further examined by the production of a cost-effectiveness acceptability curve, which demonstrates the number of times that the cost per QALY estimates for metal stents fall below different predefined cost per QALY thresholds. This shows that SEMS are unlikely to be more cost-effective than non-SEMS within the usual limits of acceptability.

Chapter 5

Summary and implications

The introduction of SEMS was hailed as a major breakthrough in the palliation of malignant dysphagia, a panacea for the inoperable patient, but this study has suggested that no single treatment can satisfy all of the criteria of an ideal treatment. This study has not conclusively demonstrated that any one of the palliative treatment modalities is in overall terms better than another, but has shown that each modality of treatment clearly has specific advantages and disadvantages. However, poor trial recruitment entailed that this study was significantly underpowered and type II error may mean that one treatment may be significantly better than the others.

Of the non-SEMS therapies, rigid intubation was the longest established and was previously the accepted standard treatment. It is still widely used worldwide and initial purchase costs are low. It is difficult to be sure of the clinical relevance of the consequent, relatively poor quality of swallowing in comparison to other available therapies in view of unaffected nutritional and quality of life parameters, but this study has certainly shown that rigid intubation confers rapid and lasting palliation of dysphagia in one endoscopic session. In contrast to previous studies, if a cautious pulsion technique is used then this is not as traumatic as expected and, as a result, associated early morbidity was comparable to other treatments. However, the late complication rate was unacceptably high, with significantly more interventions required for tube blockages and migrations. As such, although the low purchase cost means that overall costs are unaffected by the need for reintervention, the late morbidity and quality of swallowing are significant drawbacks compared with the other therapies evaluated by this study.

Other than the problems encountered with primary BICAP and ETN, the various non-stent treatments have been shown to produce extremely effective dysphagia relief, with maintenance of quality of life and low associated morbidity and mortality. The disadvantages of these therapies are the need for specialist equipment, trained personnel and time-consuming, repetitive treatments. As a result, it appears that a small volume of work rapidly overloads system availability, with subsequent significant delay to treatment and a greater need for pretreatment endoscopic dilatations temporarily to relieve dysphagia and bridge this gap. Further, the need for repeated treatments with associated transportation and hospital attendance is taxing for elderly, terminally ill patients despite being mostly performed on an outpatient basis. However, the most striking finding in relation to the non-stent therapies is the associated survival advantage. This parallels the findings of other recent studies and is a major source of concern for the future use of stent treatments. The reasons for this finding are as yet difficult to explain and this requires further *in vitro* and *in vivo* research, but may become a major factor in the choice of palliation.

The SEMS as an evolution of the rigid tube also produce rapid, effective and lasting dysphagia relief in one endoscopic session. The less traumatic insertion technique has not been shown to reduce early morbidity, but SEMS were associated with a lower late complication rate than rigid intubation and this recoups some of their high initial purchase cost. Although the 24-mm SEMS was introduced to reduce migration and improve dysphagia relief, it appears to do neither. The main disadvantage of the SEMS therapies is a significant reduction in quality of life after treatment owing to pain, which is most marked with the 24-mm SEMS. The potential for aspiration is another problem with any stent when applied across the oesophagogastric junction, with no cases of this potentially fatal complication occurring in non-stent patients. Aspiration, especially in the presence of opiate analgesia, may account for many unexplained early deaths, and it is suggested that caution should be exercised when bridging the oesophagogastric junction with any stent.

It is clear that many factors have to be considered in choosing the best palliative treatment for a patient with inoperable oesophageal cancer. The information from this study suggests that the choice lies between a non-stent treatment and the 18-mm SEMS, since rigid intubation has significant disadvantages in comparison to

these therapies and the 24-mm SEMS has been shown to have no advantage over its 18-mm counterpart. Since costs and clinical effectiveness are equivalent, individual patient and tumour characteristics must be used to determine the best treatment, as well as weighing up the expected effect of treatment and longevity. The best management of tumour types and sites must be considered, such as tumours at the oesophagogastric junction, where the mortality from aspiration associated with stent treatment is an area of concern and would be an area where a non-stent treatment may be of benefit. Similarly, many of the potential complications and pitfalls of specific therapies could be dealt with before treatment; for example, the depreciative effect on quality of life from the pain experienced by 18-mm SEMS-treated patients could be reduced by awareness of the phenomenon and adequate pretreatment analgesia. This is a pragmatic approach: some patients will benefit from one-off relief of dysphagia and minimal hospital attendance, whereas others will be content to travel for repeated treatment and improved clinical contact if the delay to treatment could be reduced. One hypothesis for the delay is that the service is overburdened. It is vitally important that this area be audited to identify where the true problem lies and whether or not the delay is simply the nature of the treatment set-up. Since making a palliative treatment decision takes into account many variables, it would seem prudent that these decisions should be made not by individual clinicians but by a multidisciplinary team and consideration of patient preferences. The health state utilities substudy clearly demonstrated that patients hold perceptions and beliefs as to the efficacy and effect of a variety of medical therapies, which could influence outcome. Patients with inoperable cancer of the oesophagus have been shown to have very poor quality of life and informed involvement in their own treatment choices is not only an individual's prerogative, but also helps to establish control over their cancer.[288,308–310]

This study can be criticised for being underpowered despite being based on a patient group five times larger than the previous best evidence base. As a result, type II error may have concealed the fact that one of the palliative treatments is indeed better than the rest. An equivalence trial would be necessary to confirm this, which would require vast numbers of patients and is simply not practical. Despite the underpowering of the study, the current practice of 'inoperable oesophageal cancer equals stent' is not justified on the basis of these findings, and the SEMS is not the panacea that it was expected to be when it was first introduced. The survival results in particular are of concern and the potential implications are such that 'inoperable oesophageal cancer equals non-stent treatment' may well be applied unless a specific reason suggests otherwise. This has serious and widespread implications to the NHS palliative set-up in terms of availability and access to non-stent treatment, as demonstrated by the significant delay to treatment in this study. However, the differences between treatments are small, and in terms of reducing the burden of palliation to the NHS this study has shown that reducing hospital stay, for example by greater community care and improved pain control, would be more likely to make an economic difference than changing treatment modalities. The finding of survival differences between treatments is also striking and warrants further investigation. This may be due to improved patient contact leading to a serendipitous effect on survival, and this contact could have quality of life effects and reduce readmission rates. An audit of palliative patient admissions would determine the reasons and need for inpatient hospital care, which could form the basis of an audit cycle with changes implemented to reduce unnecessary admissions and thus total cost burden, for example through the use of a community-based hospital liaison nurse.

In view of the underpowered nature of this study, firm conclusions cannot be justified, but this remains by far the largest RCT in this area and contributes considerable understanding that could influence clinical practice and inform treatment choice.

Conclusions

No difference was found in cost or effectiveness between SEMS and non-SEMS therapies. A survival advantage was found for non-stent therapies, but with a significant delay to treatment.

The 18-mm SEMS had equal effectiveness to, but less associated pain than 24-mm SEMS, and, rigid intubation was associated with a worse quality of swallowing and increased late morbidity. BICAP and ETN were very poor in primary palliation.

The length of hospital stay was found to account for the majority of the cost to NHS.

Implications for healthcare

It was suggested that rigid tubes and 24-mm SEMS should no longer be recommended, and that the choice in palliation lies between non-stent and 18-mm SEMS therapies. Non-stent therapies should be made more readily available and accessible to reduce delay. BICAP and ETN were not to be suitable for primary palliation.

It was also suggested that the length of stay should be targeted to reduce the NHS burden of palliation, with due regard to quality of life and costs.

Recommendations for future research

A randomised controlled clinical trial of 18-mm SEMS versus non-stent therapies considering survival and quality of life end-points would be valuable. An audit of palliative patient admissions is also suggested to determine the reasons and need for inpatient hospital care, with a view to implementing cycle-associated change to reduce inpatient stay. Delay to palliative radiotherapy treatment should also be studied, with a view to implementing cycle-associated change to reduce waiting time.

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Contributions of authors

Jon Shenfine (Research Fellow, Oesophago-Gastric Surgery) was the clinical research fellow for the study, responsible for the clinical components of the trial including drawing up of protocols, obtaining ethical approval, providing day-to-day project management, the appointment and training of the research nurses, managing data collection and maintaining standards across all centres. He also ensured compliance to research protocol in the study centres, the development and production of data-collection instruments, data entry, cleaning and validation and data analysis. He had the main responsibility for the preparation of the report.

Paul McNamee (Senior Research Fellow, University Centre for Health Services Research) was the health economist on the study and contributed to project management, the development of research protocols and data analysis and was specifically responsible for the health economic aspects of the trial. He was involved in the interpretation of the analysis and contributed to the writing of the report.

Nick Steen (Senior Medical Statistician, University Centre for Health Services Research) was the medical statistician for the study. He contributed to project management, the development of research protocols, the running of the randomisation service and data entry, cleaning and validation. He was specifically responsible for data analysis and interpretation and contributed to the writing of the report.

John Bond (Professor of Health Services Research, University Centre for Health Services Research) was one of the main study supervisors and contributed to project management, the

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S Michael Griffin (Professor of Gastrointestinal Surgery, Oesophago-Gastric Unit, Royal Victoria Infirmary) was one of the main study supervisors and the lead trial clinician. He contributed to project management, the development of research protocols, the interpretation of data and supervised the preparation of the report.

References

1. Akiyama H. *Surgery for cancer of the esophagus*. Baltimore, MD: Williams & Wilkins; 1990.
2. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma [review]. *Br J Surg* 1990;**77**:845–57.
3. Barr H, Krasner N. Prospective quality-of-life analysis after palliative photoablation for the treatment of malignant dysphagia. *Cancer* 1991; **68**:1660–4.
4. Loizou LA, Grigg D, Atkinson M, Robertson C, Bown SG. A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. *Gastroenterology* 1991; **100**:1303–10.
5. Blazeby JM, Alderson D, Farndon JR. Quality of life in patients with oesophageal cancer. *Recent Results Cancer Research* 2000;**155**:193–204.
6. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. *Int J Cancer* 1993; **55**:891–903.
7. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**:1287–9.
8. Brewster DH, Fraser LA, McKinney PA, Black RJ. Socioeconomic status and risk of adenocarcinoma of the oesophagus and cancer of the gastric cardia in Scotland. *Br J Cancer* 2000;**83**:387–90.
9. Reed PI, Johnston BJ. The changing incidence of oesophageal cancer. *Endoscopy* 1993;**25**:606–8.
10. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1990;**62**:440–3.
11. Dolan K, Sutton R, Walker SJ, Morris AI, Campbell F, Williams EM. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. *Br J Cancer* 1999;**80**:834–42.
12. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**:2049–53.
13. McKinney A, Sharp L, Macfarlane GJ, Muir CS. Oesophageal and gastric cancer in Scotland 1960–90. *Br J Cancer* 1995;**71**:411–15.
14. Office for National Statistics. *Mortality Statistics. Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 1997*. Series DH2 No. 24 (Table 3). pp. 96–7.
15. Anderson JR. Incidences of gastric and oesophageal cancer in Europe. *Scott Med J* 1998; **43**:41.
16. Allum W. Epidemiology and screening for oesophageal and gastric cancer. In Griffin SM, Raimes SA, editors. *Upper gastrointestinal surgery*. Philadelphia, PA: WB Saunders; 1997. pp. 35–58.
17. Pera M. Epidemiology of esophageal cancer, especially adenocarcinoma of the esophagus and esophagogastric junction. *Recent Results Cancer Res* 2000;**155**:1–14.
18. Allum WH. Combination chemotherapy with epirubicin, cisplatin and 5-fluorouracil for the palliation of advanced gastric and oesophageal adenocarcinoma. The MRC Gastric Cancer Working Party and the British Stomach Cancer Group [letter; comment]. *Br J Surg* 1995;**82**:565.
19. Day NE. The geographic pathology of cancer of the oesophagus. *Br Med Bull* 1984;**40**:329–34.
20. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–31.
21. Griffith JL, Davis JT. A twenty-year experience with surgical management of carcinoma of the esophagus and gastric cardia. *J Thorac Cardiovasc Surg* 1980;**79**:447–52.
22. Schuchmann GF, Heydorn WH, Hall RV, Carter SC, Gillespie JT, Grishkin BA, *et al*. Treatment of esophageal carcinoma: a retrospective review. *J Thorac Cardiovasc Surg* 1980;**79**:67–73.
23. Launois B, Paul JL, Lygidakis NJ, Campion JP, Malledant Y, Grossetti D, *et al*. Results of the surgical treatment of carcinoma of the esophagus. *Surgery, Gynecology and Obstetrics* 1983;**156**:753–60.
24. Benasco C, Combalia N, Pou JM, Miquel JM. Superficial esophageal carcinoma: a report of 12 cases. *Gastrointest Endosc* 1985;**31**:64–7.
25. Watkinson AF, Ellul J, Entwisle K, Mason RC, Adam A. Esophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprostheses. *Radiology* 1995;**195**:821–7.

26. Martin IG, Young S, Sue-Ling H, Johnston D. Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. *BMJ* 1997; **314**:467.

27. Wayman J, Raimes S, Griffin SM, Hayes N. Delays in diagnosing oesophagogastric cancer. Small study found that four fifths of delay was due to patients. *BMJ* 1997;**315**:428.

28. Sagar P, Gauperaa T, Sue-Ling H, McMahon M, Johnston D. An audit of the treatment of cancer of the oesophagus. *Gut* 1994;**35**:941–5.

29. Clinical Outcomes Group, NHS Executive. *Improving the outcomes in upper gastro-intestinal cancers: the research evidence*. London: Department of Health; 2001.

30. Dresner SM, Lamb PJ, Bennett MK, Hayes N, Griffin SM. The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. *Surgery* 2001;**129**:103–9.

31. Stein HJ, Sendler A, Fink U, Siewert JR. Multidisciplinary approach to esophageal and gastric cancer. *Surg Clin North Am* 2000;**80**:659–82; Discussions 683–6.

32. Clark GW, Roy MK, Corcoran BA, Carey PD. Carcinoma of the oesophagus: the time for a multidiciplinary approach? *Surg Oncol* 1996; **5**:149–64.

33. Hennessy T. Cancer of the oesophagus. *Postgrad Med J* 1996;**72**:458–63.

34. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery [review]. *Br J Surg* 1980;**67**:381–90.

35. Tekkis PP, Kocher HM, Bentley AJ, Cullen PT, South LM, Trotter GA, *et al.* Operative mortality rates among surgeons: comparison of POSSUM and p-POSSUM scoring systems in gastrointestinal surgery. *Dis Colon Rectum* 2000;**43**:1528–32; Discussion 1532–4.

36. Dresner SM, Lamb PJ, Shenfine J, Hayes N, Griffin SM. Prognostic significance of peri-operative blood transfusion following radical resection for oesophageal carcinoma. *Eur J Surg Oncol* 2000;**26**:492–7.

37. Oliver S, Robertson C, Logan R. Oesophageal cancer: a population-based study of survival after treatment. *Br J Surg* 1992;**79**:1321–5.

38. Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer* 2000;**88**:1781–7.

39. Lambert R. Palliation of carcinoma of the esophagus: is there a hope for cure? [review]. *Am J Gastroenterol* 1994;**89** (8 Suppl):S27–40.

40. O'Hanlon DM, Callanan K, Karat D, Crisp W, Griffin SM. Outcome, survival, and costs in patients undergoing intubation for carcinoma of the esophagus. *Am J Surg* 1997;**174**:316–19.

41. Blazeby JM, Williams MH, Brookes ST, Alderson D, Farndon JR. Quality of life measurement in patients with oesophageal cancer. *Gut* 1995;**37**:505–8.

42. Fleischer D, Kessler F. Endoscopic Nd:YAG laser therapy for cancer of the oesophagus: a new form of palliative treatment. *Gastroenterology* 1983; **85**:600–6.

43. Mason R. Palliation of malignant dysphagia: an alternative to surgery. *Ann R Coll Surg Engl* 1996;**78**:457–62.

44. Overholt BF. Laser and photodynamic therapy of esophageal cancer [review]. *Semin Surg Oncol* 1992;**8**:191–203.

45. Radford CM, Ahlquist DA, Gostout CJ, Viggiano TR, Balm RK, Zinsmeister AR. Prospective comparison of contact with noncontact Nd:Yag laser therapy for palliation of esophageal carcinoma. *Gastrointest Endosc* 1989;**35**:394–7.

46. Krasner N, Barr H, Skidmore C, Morris AI. Palliative laser therapy for malignant dysphagia. *Gut* 1987;**28**:792–8.

47. Shmueli E, Myszor MF, Burke D, Record CO, Matthewson K. Limitations of laser treatment for malignant dysphagia. *Br J Surg* 1992;**79**:778–80.

48. Bourke MJ, Hope RL, Chu G, Gillespie PE, Bull C, O'Rourke I, *et al*. Laser palliation of inoperable malignant dysphagia: initial and at death. *Gastroint Endosc* 1996;**43**:29–32.

49. Savage A, Baigrie R, Cobb R, Barr H, Kettlewell M. Palliation of malignant dysphagia by laser therapy. *Dis Esophagu*s 1997;**10**:243–6.

50. Abdel-Wahab M, Gad-Elhak N, Denewer A, El-Ebidy G, Sultan A, Abou-Elenin A, *et al*. Endoscopic laser treatment of progressive dysphagia in patients with advanced esophageal carcinoma. *Hepatogastroenterology* 1998;**45**:1509–15.

51. Norberto L, Ranzato R, Marino S, Angriman I, Erroi F, Donadi M, *et al*. Endoscopic palliation of esophageal and cardial cancer: neodymium–yttrium aluminum garnet laser therapy. *Dis Esophagus* 1999;**12**:294–6.

52. Fleischer D. A comparison of endoscopic laser therapy and BICAP tumor probe therapy for esophageal cancer. *Am J Gastroenterol* 1987; **82**:608–12.

53. Hurley J, Cade RJ. Laser photocoagulation in the treatment of malignant dysphagia. *Australian and New Zealand Journal of Surgery* 1997;**67**:800–3.

54. Mathus-Vliegen EM, Tytgat GN. Analysis of failures and complications of neodymium: YAG laser photocoagulation in gastrointestinal tract

tumors. A retrospective survey of 18 years' experience [review]. *Endoscopy* 1990;**22**:17–23.

55. Robertson C, Griffith C, Atkinson M, Hardcastle J. Pseudoachalasia of the cardia – a review. *J R Soc Med* 1988;**88**:399–402.

56. Narayan S, Sivak MV Jr. Palliation of esophageal carcinoma. Laser and photodynamic therapy. [review]. *Chest Surg Clin N Am* 1994;**4**:347–67.

57. Mellow MH, Pinkas H. Endoscopic therapy for esophageal carcinoma with Nd:YAG laser: prospective evaluation of efficacy, complications, and survival. *Gastrointest Endosc* 1984;**30**:334–9.

58. Sargeant IR, Loizou LA, Tobias JS, Blackman G, Thorpe S, Bown SG. Radiation enhancement of laser palliation for malignant dysphagia: a pilot study. *Gut* 1992;**33**:1597–601.

59. Shmueli E, Srivastava E, Dawes PJ, Clague M, Matthewson K, Record CO. Combination of laser treatment and intraluminal radiotherapy for malignant dysphagia. *Gut* 1996;**38**:803–5.

60. Cottier D, Carter C, Smith J, Anderson J. The combination of laser recanalization and endoluminal intubation in the palliation of malignant dysphagia. *J R Coll Surg Edinb* 1997; **42**:19–20.

61. Sargeant IR, Loizou LA, Tulloch M, Thorpe S, Brown SG. Recanalization of tube overgrowth: a useful new indication for laser in palliation of malignant dysphagia. *Gastrointest Endosc* 1992; **38**:165–9.

62. Johanns W, Luis W, Jansen J, Kahl S, Greiner L. Argon plasma coagulation (APC) in gastroenterology: experimental and clinical experiences. *Eur J Gastroenterol Hepatol* 1997; **9**:581–7.

63. Watson J, Bennett M, Griffin S, Matthewson K. The tissue effect of argon plasma coagulation on esophageal and gastric mucosa. *Gastrointest Endosc* 2000;**52**:342–5.

64. Byrne J, Armstrong G, Attwood S. Restoration of the normal squamous lining in Barrett's esophagus by argon beam plasma coagulation. *Am J Gastroeneterology* 1998;**93**:1810–15.

65. Robertson G, Thomas M, Jamieson J, Veitch P, Dennison A. Palliation of oesophageal cancer using the argon beam coagulator. *Br J Surg* 1996;**83**:1769–71.

66. Heindorff H, Wojdemann M, Bisgaard T, Svendsen LB. Endoscopic palliation of inoperable cancer of the oesophagus or cardia by argon electrocoagulation. *Scand J Gastroenterol* 1998;**33**: 21–3.

67. Wahab P, Mulder C, den Hartog G, Thies J. Argon plasma coagulation in flexible gastrointestinal endoscopy: pilot experiences. *Endoscopy* 1997;**29**:176–81.

68. Bown SG. Palliation of malignant dysphagia: surgery, radiotherapy, laser, intubation alone or in combination? *Gut* 1991;**32**:841–4.

69. Tyrell M, Trotter G, Adam A, Mason R. Incidence and management of laser-associated oesophageal perforation. *Br J Surg* 1995;**82**:1257–8.

70. Niezychowski W, Regula J, Fijuth J, Przytulski K, Butruk E. Argon plasma coagulation in palliative treatment of malignant dysphagia. *Gut* 1996; **39** (Suppl 3):A5.

71. May A, Selmaier M, Hochberger J, Gossner L, Muhldorfer S, Hahn EG, *et al*. Memory metal stents for palliation of malignant obstruction of the oesophagus and cardia. *Gut* 1995;**37**:309–13.

72. Bramhall SR, Veitch PS, Gourevitch D, Wicks AC. An improved method for oesophageal intubation. *Ann R Coll Surg Engl* 1993;**75**:189–92.

73. Barr H, Krasner N, Raouf A, Walker RJ. Prospective randomised trial of laser therapy only and laser therapy followed by endoscopic intubation for the palliation of malignant dysphagia. *Gut* 1990;**31**:252–8.

74. McIntyre AS, Morris DL, Sloan RL, Robertson CS, Harrison J, Burnham WR, *et al*. Palliative therapy of malignant esophageal stricture with the bipolar tumor probe and prosthetic tube. *Gastrointest Endosc* 1989;**35**:531–5.

75. Johnston JH, Fleischer D, Petrini J, Nord HJ. Palliative bipolar electrocoagulation therapy of obstructing esophageal cancer. *Gastrointest Endosc* 1987;**33**:349–53.

76. Jensen DM, Machicado G, Randall G, Tung LA, English-Zych S. Comparison of low-power YAG laser and BICAP tumor probe for palliation of esophageal cancer strictures. *Gastroenterology* 1988;**94**:1263–70.

77. Conio M, Bonelli L, Martines H, Munizzi F, Aste H. Palliative bipolar electrocoagulation treatment of malignant gastroesophageal strictures. *Surg Endosc* 1990;**4**:164–7.

78. Maunoury V, Brunetaud JM, Cochelard D, Boniface B, Cortot A, Paris JC. Endoscopic palliation for inoperable malignant dysphagia: long term follow up. *Gut* 1992;**33**:1602–7.

79. Heier SK, Rothman KA, Heier LM, Rosenthal WS. Photodynamic therapy for obstructing esophageal cancer: light dosimetry and randomised comparison with Nd:YAG laser therapy. *Gastroenterology* 1995;**109**:63–72.

80. Luketich JD, Nguyen NT, Weigel TL, Keenan RJ, Ferson PF, Belani CP. Photodynamic therapy for treatment of malignant dysphagia. *Surg Laparosc Endosco Percutan Tech* 1999;**9**:171–5.

81. Lightdale CJ, Heier SK, Marcon NE, McCaughan JS, Gerdes H, Overholt BF, *et al*.

Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. *Gastrointest Endosc* 1995; **42**:507–12.

82. Thomas RJ, Abbott M, Bhathal PS, St John DJB, Morstyn G. High-dose photoirradiation of esophageal cancer. *Ann Surg* 1987;**206**:193–9.

83. McCaughan JS, Ellison EC, Guy JT, Hicks WJ, Jones JJ, Laufman LR, *et al*. Photodynamic therapy for esophageal malignancy: a prospective twelve-year study. *Ann Thorac Surg* 1996;**62**: 1005–9; Discussion 1009–10.

84. Maier A, Tomaselli F, Gebhard F, Rehak P, Smolle J, Smolle-Juttner F. Palliation of advanced esophageal carcinoma by photodynamic therapy and irradiation. *Ann Thorac Surg* 2000;**69**:1006–9.

85. Moghissi K, Dixon K, Thorpe JA, Stringer M, Moore PJ. The role of photodynamic therapy (PDT) in inoperable oesophageal cancer. *Eur J Cardiothorac Surg* 2000;**17**:95–100.

86. Chung SC, Leong HT, Choi CY, Leung JW, Li AK. Palliation of malignant oesophageal obstruction by endoscopic alcohol injection. *Endoscopy* 1994; **26**:275–7.

87. Nwokolo CU, Payne-James JJ, Silk DB, Misiewicz JJ, Loft DE. Palliation of malignant dysphagia by ethanol induced tumour necrosis. *Gut* 1994;**35**:299–303.

88. Moreira LS, Coelho RC, Sadala RU, Dani R. The use of ethanol injection under endoscopic control to palliate dysphagia caused by esophagogastric cancer. *Endoscopy* 1994;**26**:311–14.

89. Wright RA, O'Conner KW. A pilot study of endoscopic injection chemo/sclerotherapy of esophageal carcinoma. *Gastrointest Endosc* 1990; **36**:47–8.

90. Monga S, Wadleigh R, Sharma A, Adib H, Strader D, Singh G, *et al*. Intratumoral therapy of cisplatin/epinephrine injectable gel for palliation in patients with obstructive esophageal cancer. *Am J Clin Oncol* 2000;**23**:386–92.

91. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, *et al*. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Eng J Med* 1992;**326**:1593–8.

92. Coia LR, Minsky BD, John MJ, Haller DG, Landry J, Pisansky TM, *et al*. The evaluation and treatment of patients receiving radiation therapy for carcinoma of the esophagus: results of the 1992–1994 Patterns of Care Study. *Cancer* 1999; **85**:2499–505.

93. Coia LR, Paul AR, Engstrom PF. Combined radiation and chemotherapy as primary management of adenocarcinoma of the esophagus and gastroesophageal junction. *Cancer* 1988; **61**:643–9.

94. Coia LR, Engstrom PF, Paul AR, Stafford PM, Hanks GE. Long-term results of infusional 5-FU, mitomycin-C and radiation as primary management of esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1991;**20**:29–36.

95. Agrawal RK, Dawes PJ, Clague MB. Combined external beam and intracavitary radiotherapy in oesophageal carcinoma. *Clin Oncol (R Coll Radiol)* 1992;**4**:222–7.

96. Pearson JG. Radiotherapy for esophageal carcinoma. *World J Surg* 1981;**5**:489–97.

97. Stoller JL, Brumwell ML. Palliation after operation and after radiotherapy for cancer of the esophagus. *Can J Surg* 1984;**27**:491–5.

98. Langer M, Choi NC, Orlow E, Grillo H, Wilkins EW Jr. Radiation therapy alone or in combination with surgery in the treatment of carcinoma of the esophagus. *Cancer* 1986;**58**:1208–13.

99. Albertsson M, Ewers SB, Widmark H, Hambraeus G, Lillo-Gil R, Ranstam J. Evaluation of the palliative effect of radiotherapy for esophageal carcinoma. *Acta Oncol* 1989;**28**:267–70.

100. Caspers RJ, Welvaart K, Verkes RJ, Hermans J, Leer JW. The effect of radiotherapy on dysphagia and survival in patients with esophageal cancer. *Radiother Oncol* 1988;**12**:15–23.

101. Petrovich Z, Langholz B, Formenti S, Luxton G, Astrahan M. Management of carcinoma of the esophagus: the role of radiotherapy. *Am J Clin Oncol* 1991;**14**:80–6.

102. Kelsen D. Treatment of advanced esophageal cancer. *Cancer* 1982;**50** (11 Suppl):2576–81.

103. Siersema PD, Dees J, van Blankenstein M. Palliation of malignant dysphagia from oesophageal cancer. Rotterdam Oesophageal Tumor Study Group [review]. *Scand J Gastroenterol Suppl* 1998;**225**:75–84.

104. Ng TM, Spencer GM, Sargeant IR, Thorpe SM, Bown SG. Management of strictures after radiotherapy for esophageal cancer. *Gastrointest Endosc* 1996;**43**:584–90.

105. Swaroop VS, Desai DC, Mohandas KM, Dhir V, Dave UR, Gulla RI, *et al*. Dilation of esophageal strictures induced by radiation therapy for cancer of the esophagus. *Gastrointest Endosc* 1994;**40**:311–15.

106. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoms: II. A critical view of radiotherapy [review]. *Br J Surg* 1980;**67**:457–61.

107. De Paoli A, Boz G, Trovo MG, Franchin G, Roncadin M, Talamini R, *et al*. Multiple fraction per day radiation therapy for inoperable

esophageal cancer. *Int J Radiat Oncol Biol Phys* 1988;**14**:855–60.

108. Sur RK, Donde B, Levin VC, Mannell A. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 1998;**40**:447–53.

109. Rowland CG, Pagliero KM. Intracavitary irradiation in palliation of carcinoma of oesophagus and cardia. *Lancet* 1985;**ii**:981–3.

110. Fleischman EH, Kagan AR, Bellotti JE, Streeter OE Jr, Harvey JC. Effective palliation for inoperable esophageal cancer using intensive intracavitary radiation. *J Surg Oncol* 1990;**44**:234–7.

111. Jager J, Langendijk H, Pannebakker M, Rijken J, de Jong J. A single session of intraluminal brachytherapy in palliation of oesophageal cancer. *Radiother Oncol* 1995;**37**:237–40.

112. Harvey JC, Fleischman EH, Bellotti JE, Kagan AR. Intracavitary radiation in the treatment of advanced esophageal carcinoma: a comparison of high dose rate vs. low dose rate brachytherapy. *J Surg Oncol* 1993;**52**:101–4.

113. Brewster AE, Davidson SE, Makin WP, Stout R, Burt PA. Intraluminal brachytherapy using the high dose rate microSelectron in the palliation of carcinoma of the oesophagus. *Clin Oncol (R Coll Radiol)* 1995;**7**:102–5.

114. Hyden EC, Langholz B, Tilden T, Lam K, Luxton G, Astrahan M, *et al*. External beam and intraluminal radiotherapy in the treatment of carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988;**96**:237–41.

115. Taal BG, Aleman BM, Koning CC, Boot H. High dose rate brachytherapy before external beam irradiation in inoperable oesophageal cancer. *Br J Cancer* 1996;**74**:1452–7.

116. Caspers RJ, Zwinderman AH, Griffioen G, Welvaart K, Sewsingh EN, Davelaar J, *et al*. Combined external beam and low dose rate intraluminal radiotherapy in oesophageal cancer. *Radiother Oncol* 1993;**27**:7–12.

117. Flores AD, Nelems B, Evans K, Hay JH, Stoller J, Jackson SM. Impact of new radiotherapy modalities on the surgical management of cancer of the esophagus and cardia. *Int J Radiat Oncol Biol Phys* 1989;**17**:937–44.

118. Jager JJ, Pannebakker M, Rijken J, de Vos J, Vismans FJ. Palliation in esophageal cancer with a single session of intraluminal irradiation. *Radiother Oncol* 1992;**25**:134–6.

119. Pakisch B, Kohek P, Poier E, Stucklschweiger G, Poschauko J, Raith J, *et al*. Iridium-192 high dose rate brachytherapy combined with external beam irradiation in non-resectable oesophageal cancer. *Clin Oncol (R Coll Radiol)* 1993;**5**:154–8.

120. van Riel JM, van Groeningen CJ. Palliative chemotherapy in advanced gastrointestinal cancer [review]. *Eur J Gastroenterol Hepatol* 2000;**12**:391–6.

121. De Besi P, Sileni VC, Salvagno L, Tremolada C, Cartei G, Fosser V, *et al*. Phase II study of cisplatin, 5-FU, and allopurinol in advanced esophageal cancer. *Cancer Treatment Reports* 1986;**70**:909–10.

122. Levard H, Pouliquen X, Hay JM, Fingerhut A, Langlois-Zantain O, Huguier M, *et al*. 5-Fluorouracil and cisplatin as palliative treatment of advanced oesophageal squamous cell carcinoma. A multicentre randomised controlled trial. The French Associations for Surgical Research. *Eur J Surg* 1998;**164**:849–57.

123. Thomas AL, O'Byrne K, Steward WP. Chemotherapy for upper gastrointestinal tumours [review]. *Postgrad Med J* 2000;**76**:321–7.

124. Advani SH, Saikia TK, Swaroop S, Ramakrishnan G, Nair CN, Dinshaw KA, *et al*. Anterior chemotherapy in esophageal cancer. *Cancer* 1985; **56**:1502–6.

125. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, *et al*. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer* 1997;**33**:1216–20.

126. Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC. A phase II evaluation of high dose cisplatin and etoposide in patients with advanced esophageal adenocarcinoma. *Cancer* 1996;**78**:2070–7.

127. Highley MS, Parnis FX, Trotter GA, Houston SJ, Penson RT, Harper PG, *et al*. Combination chemotherapy with epirubicin, cisplatin and 5-fluorouracil for the palliation of advanced gastric and oesophageal adenocarcinoma. *Br J Surg* 1994;**81**:1763–5.

128. Ajani JA, Ilson DH, Kelsen DP. Paclitaxel in the treatment of patients with upper gastrointestinal carcinomas. *Semin Oncol* 1996;**23** (5 Suppl 12):55–8.

129. Coia LR, Engstrom PF, Paul A. Nonsurgical management of esophageal cancer: report of a study of combined radiotherapy and chemotherapy. *J Clin Oncol* 1987;**5**:1783–90.

130. Coia LR, Soffen EM, Schultheiss TE, Martin EE, Hanks GE. Swallowing function in patients with esophageal cancer treated with concurrent radiation and chemotherapy. *Cancer* 1993; **71**:281–6.

131. Calais G, Dorval E, Louisot P, Bourlier P, Klein V, Chapet S, *et al*. Radiotherapy with high dose rate brachytherapy boost and concomitant chemotherapy for Stages IIB and III esophageal carcinoma: results of a pilot study. *Int J Radiat Oncol Biol Phys* 1997;**38**:769–75.

132. Parker CH, Peura DA. Palliative treatment of esophageal carcinoma using esophageal dilation and prosthesis [review]. *Gastroenterol Clin North Am* 1991;**20**:717–29.

133. Lundell L, Leth R, Lind T, Lonroth H, Sjovall M, Olbe L. Palliative endoscopic dilatation in carcinoma of the esophagus and esophagogastric junction. *Acta Chir Scand* 1989;**155**:179–84.

134. Tytgat GN, den Hartog Jager FC. To dilate or to intubate? [editorial]. *Gastrointest Endosc* 1983;**29**:58–9.

135. Heit HA, Johnson LF, Siegel SR, Boyce HW Jr. Palliative dilation for dysphagia in esophageal carcinoma. *Ann Intern Med* 1978;**89**:629–31.

136. Souttar H. A method of intubating the oesophagus for malignant stricture. *Br J Surg* 1924;**1**:782–3.

137. Das SK, John HT. Oesophageal intubation in obstructive lesions of the oesophagus. *Br J Surg* 1973;**60**:403–6.

138. Anscombe AR, Pearson K, Taylor TV. A simple method for the introduction of an oesophageal tube in advanced carcinoma of the oesophagus. *Br J Surg* 1976;**63**:947–8.

139. Atkinson M, Ferguson R, Parker GC. Tube introducer and modified Celestin tube for use in palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. *Gut* 1978; **19**:669–71.

140. Lishman AH, Dellipiani AW, Devlin HB. The insertion of oesophagogastric tubes in malignant oesophageal strictures: endoscopy or surgery? *Br J Surg* 1980;**67**:257–9.

141. Tan BS, Mason RC, Adam A. Minimally invasive therapy for advanced oesophageal malignancy [review]. *Clin Radiol* 1996;**51**:828–36.

142. Watson A. A study of the quality and duration of survival following resection, endoscopic intubation and surgical intubation in oesophageal carcinoma. *Br J Surg* 1982;**69**:585–8.

143. Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. *Gut* 1982;**23**:1060–7.

144. Kratz JM, Reed CE, Crawford FA, Stroud MR, Parker EF. A comparison of endoesophageal tubes. Improved results with the Atkinson tube. *J Thorac Cardiovasc Surg* 1989;**97**:19–23.

145. Tytgat GN, den Hartog Jager FC, Haverkamp J. Positioning of a plastic prosthesis under fiberendoscopic control in the palliative treatment of cardioesophageal cancer. *Endoscopy* 1976; **8**:180.

146. Pfleiderer AG, Goodall P, Holmes GK. The consequences and effectiveness of intubation in the palliation of dysphagia due to benign and malignant strictures affecting the oesophagus. *Br J Surg* 1982;**69**:356–8.

147. Jones DB, Davies PS, Smith PM. Endoscopic insertion of palliative oesophageal tubes in oesophagogastric neoplasms. *Br J Surg* 1981; **68**:197–8.

148. Ell C, May A. Self-expanding metal stents for palliation of stenosing tumors of the esophagus and cardia: a critical review [review]. *Endoscopy* 1997;**29**:392–8.

149. Spinelli P, Cerrai F, Dal-Fente M, Mancini A, Meroni E, Pizzetti P. Endoscopic treatment of upper gastrointestinal tract malignancies. *Endoscopy* 1993;**25**:675–8.

150. Reed CE. Endoscopic palliation of esophageal carcinoma [review]. *Chest Surg Clin N Am* 1994; **4**:155–72.

151. den Hartog Jager FC, Bartelsman JF, Tytgat GN. Palliative treatment of obstructing esophagogastric malignancy by endoscopic positioning of a plastic prosthesis. *Gastroenterology* 1979;**77**:1008–14.

152. Angorn IB, Hegarty MM. Palliative pulsion intubation in oesophageal carcinoma. *Ann R Coll Surg Engl* 1979;**61**:212–14.

153. Maydeo AP, Bapaye A, Desai PN, Khanna SS, Deshpande RK, Badve R. Endoscopic placement of indigenous plastic esophageal endoprostheses – does it still have a role in the era of expandable metallic stents? A prospective Indian study in 265 consecutive patients. *Endoscopy* 1998;**30**:532–7.

154. Reed C. Comparison of different treatments for unresectable esophageal cancer. *World J Surg* 1995;**19**:828–35.

155. Unruh HW, Pagliero KM. Pulsion intubation versus traction intubation for obstructing carcinomas of the esophagus. *Ann Thorac Surg* 1985;**40**:337–42.

156. Girardet R, Ransdell HJ, Wheat MJ. Palliative intubation in the management of esophageal carcinoma. *Ann Thorac Surg* 1974;**18**:417–30.

157. Hegarty MM, Angorn IB, Bryer JV, Henderson BJ, Le Roux BT, Logan A. Pulsion intubation for palliation of carcinoma of the oesophagus. *Br J Surg* 1977;**64**:160–5.

158. Fulton RL, Garrison RN, Polk HC Jr. The nonoperative approach to esophageal perforation due to celestin tube placement. *Arch Surg* 1979;**114**:90–1.

159. Tytgat GN, Tytgat S. Esophageal endoprosthesis in malignant stricture [review]. *J Gastroenterol* 1994; **29** (Suppl 7):80–4.

160. Gasparri G, Casalegno PA, Camandona M, Dei Poli M, Salizzoni M, Ferrarotti G, *et al*.

Endoscopic insertion of 248 prostheses in inoperable carcinoma of the esophagus and cardia: short-term and long-term results. *Gastrointest Endosc* 1987;**33**:354–6.

161. Diamantes T, Mannell A. Oesophageal intubation for advanced oesophageal cancer: the Baragwanath experience 1977–1981. *Br J Surg* 1983;**70**:555–7.

162. Schumacher B, Lubke H, Frieling T, Haussinger D, Niederau C. Palliative treatment of malignant esophageal stenosis: experience with plastic versus metal stents. *Hepatogastroenterology* 1998; **45**:755–60.

163. Oliver SE, Robertson CS, Logan RF, Sokal M, Pearson JC, Atkinson M. What does radiotherapy add to survival over endoscopic intubation alone in inoperable squamous cell oesophageal cancer? *Gut* 1990;**31**:750–2.

164. Alberts AS, Burger W, Greeff F, Schoeman L, Friediger D, Nel J, *et al*. Severe complications of 5-fluorouracil and cisplatin with concomitant radiotherapy in inoperable non-metastatic squamous cell oesophageal cancer after intubation – early termination of a prospective randomised trial [letter]. *Eur J Cancer* 1992; **28A**:1005–6.

165. Reed CE, Marsh WH, Carlson LS, Seymore CH, Kratz JM. Prospective, randomized trial of palliative treatment for unresectable cancer of the esophagus. *Ann Thorac Surg* 1991;**51**:552–5; Discussion 556.

166. Schmid EU, Alberts AS, Greeff F, Terblanche AP, Schoeman L, Burger W, *et al*. The value of radiotherapy or chemotherapy after intubation for advanced esophageal carcinoma – a prospective randomized trial. *Radiother Oncol* 1993; **28**:27–30.

167. Tytgat GN, den Hartog Jager FC, Bartelsman JF. Endoscopic prosthesis for advanced esophageal cancer. *Endoscopy* 1986;**18**:32–9.

168. Loizou LA, Rampton D, Bown SG. Treatment of malignant strictures of the cervical esophagus by endoscopic intubation using modified endoprostheses. *Gastrointest Endosc* 1992;**38**:158–64.

169. Ramanaden DN, Crimmins R, Smith PM. Atkinson tubes are a good cost-effective means of palliating inoperable oesophageal malignant strictures: an eight-year experience. *Eur J Gastroenterol Hepatol* 2000;**12**:751–3.

170. Bethge N, Knyrim K, Wagner HJ, Starck E, Pausch J, Kleist DV. Self-expanding metal stents for palliation of malignant esophageal obstruction – a pilot study of eight patients. *Endoscopy* 1992; **24**:411–15.

171. Kozarek RA. Use of expandable stents for esophageal and biliary stenoses [review]. *Gastroenterologist* 1994;**2**:264–72.

172. Lambert R. Esophageal cancer: which stent, who places it, and where? *Endoscopy* 1995;**27**:509–11.

173. Christie N, Buenaventura P, Fernando H, Nguyen N, Weigel T, Ferson P, *et al*. Results of expandable metal stents for malignant esophageal obstruction in 100 patients: short-term and long-term follow-up. *Ann Thorac Surg* 2001; **71**:1797–802.

174. Siersema PD, Hop WC, van Blankenstein M, Dees J. A new design metal stent (Flamingo stent) for palliation of malignant dysphagia: a prospective study. The Rotterdam Esophageal Tumor Study Group. *Gastrointest Endosc* 2000; **51**:139–45.

175. May A, Feess G, Bauer R, Ell C. Mucosal strangulation due to self-expanding coil stents. *Gastrointest Endosc* 1997;**46**:273–6.

176. Dicle O, Goktay AY, Akbaylar H. Palliation of malignant esophageal strictures: initial results with self-expanding uncovered nitinol coil stents. *Eur Radiol* 1999;**9**:1418–22.

177. Goldin E, Beyar M, Safra T, Globerman O, Craciun I, Wengrower D, *et al*. A new self-expandable, nickel–titanium coil stent for esophageal obstruction: a preliminary report. *Gastrointest Endosc* 1994;**40**:64–8.

178. Loser C, Folsch UR. Self-expanding metallic coil stents for palliation of esophageal carcinoma: two cases of decisive stent dysfunction. *Endoscopy* 1996;**28**:514–17.

179. Raijman I, Siddique I, Lynch P. Does chemoradiation therapy increase the incidence of complications with self-expanding coated stents in the management of malignant esophageal strictures? *Am J Gastroenterol* 1997;**92**:2192–6.

180. Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med* 1993; **329**:1302–7.

181. Ellul JP, Watkinson A, Khan RJ, Adam A, Mason RC. Self-expanding metal stents for the palliation of dysphagia due to inoperable oesophageal carcinoma. *Br J Surg* 1995; **82**:1678–81.

182. Saxon RR, Barton RE, Katon RM, Petersen BD, Lakin PC, Timmermans H, *et al*. Treatment of malignant esophageal obstructions with covered metallic Z stents: long-term results in 52 patients. *J Vasc Interv Radiol* 1995;**6**:747–54.

183. De Palma GD, di Matteo E, Romano G, Fimmano A, Rondinone G, Catanzano C. Plastic prosthesis versus expandable metal stents for palliation of inoperable esophageal thoracic carcinoma: a controlled prospective study. *Gastrointest Endosc* 1996;**43**:478–82.

184. Kozarek RA, Ball TJ, Brandabur JJ, Patterson DJ, Low D, Hill L, *et al*. Expandable versus conventional esophageal prostheses: easier insertion may not preclude subsequent stent-related problems. *Gastrointest Endosc* 1996; **43**:204–8.

185. Moores DW, Ilves R. Treatment of esophageal obstruction with covered, self-expanding esophageal Wallstents. *Ann Thorac Surg* 1996; **62**:963–7.

186. May A, Hahn EG, Ell C. Self-expanding metal stents for palliation of malignant obstruction in the upper gastrointestinal tract. Comparative assessment of three stent types implemented in 96 implantations. *J Clin Gastroenterol* 1996;**22**:261–6.

187. Feins RH, Johnstone DW, Baronos ES, O'Neil SM. Palliation of inoperable esophageal carcinoma with the Wallstent endoprosthesis. *Ann Thorac Surg* 1996;**62**:1603–7.

188. Kinsman KJ, DeGregorio BT, Katon RM, Morrison K, Saxon RR, Keller FS, *et al*. Prior radiation and chemotherapy increase the risk of life-threatening complications after insertion of metallic stents for esophagogastric malignancy. *Gastrointest Endosc* 1996;**43**:196–203.

189. Schmassmann A, Meyenberger C, Knuchel J, Binek J, Lammer F, Kleiner B, *et al*. Self-expanding metal stents in malignant esophageal obstruction: a comparison between two stent types. *Am J Gastroenterol* 1997;**92**:400–6.

190. Wengrower D, Fiorini A, Valero J, Waldbaum C, Chopita N, Landoni N, *et al*. EsophaCoil: long-term results in 81 patients. *Gastrointest Endosc* 1998;**48**:376–82.

191. Davies N, Thomas HG, Eyre-Brook IA. Palliation of dysphagia from inoperable oesophageal carcinoma using Atkinson tubes or self-expanding metal stents. *Ann R Coll Surg Engl* 1998;**80**:394–7.

192. Cowling MG, Hale H, Grundy A. Management of malignant oesophageal obstruction with self-expanding metallic stents. *Br J Surg* 1998; **85**:264–6.

193. Lam YH, Chan A, Lau J, Lee D, Ng E, Wong S, *et al*. Self-expandable metal stents for malignant dysphagia. *Australian and New Zealand Journal of Surgery* 1999;**69**:668–71.

194. Olsen E, Thyregaard R, Kill J. Esophacoil expanding stent in the management of patients with nonresectable malignant esophageal or cardiac neoplasm: a prospective study. *Endoscopy* 1999;**31**:417–20.

195. Toikkanen VJ, Nemlander AT, Ramo OJ, Salminen JT, Pekkanen AJ, Isolauri JO, *et al*. Expandable metallic stents in the management of malignant oesophageal obstruction. *Ann Chir Gynaecol* 2000;**89**:20–3.

196. 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**: 243–8.

197. Bartelsman JF, Bruno MJ, Jensema AJ, Haringsma J, Reeders JW, Tytgat GN. Palliation of patients with esophagogastric neoplasms by insertion of a covered expandable modified Gianturco-Z endoprosthesis: experiences in 153 patients. *Gastrointest Endosc* 2000;**51**:134–8.

198. Christie NA, Buenaventura PO, Fernando HC, Nguyen NT, Weigel TL, Ferson PF, *et al*. Results of expandable metal stents for malignant esophageal obstruction in 100 patients: short-term and long-term follow-up. *Ann Thorac Surg* 2001;**71**:1797–801; Discussion 1801–2.

199. Miyayama S, Matsui O, Kadoya M, Yoshikawa J, Gabata T, Kitagawa K, *et al*. Malignant esophageal stricture and fistula: palliative treatment with polyurethane-covered Gianturco stent. *J Vasc Interv Radiol* 1995;**6**:243–8.

200. Song HY, Do YS, Han YM, Sung KB, Choi EK, Sohn KH, *et al*. Covered, expandable esophageal metallic stent tubes: experiences in 119 patients. *Radiology* 1994;**193**:689–95.

201. Sanyika C, Corr P, Haffejee A. Palliative treatment of oesophageal carcinoma–efficacy of plastic versus self-expandable stents. *S Afr Med J* 1999; **89**:640–3.

202. Winkelbauer FW, Schofl R, Niederle B, Wildling R, Thurnher S, Lammer J. Palliative treatment of obstructing esophageal cancer with nitinol stents: value, safety, and long-term results. *AJR Am J Roentgenol* 1996;**166**:79–84.

203. Ell C, Hochberger J, May A, Fleig WE, Hahn EG. Coated and uncoated self-expanding metal stents for malignant stenosis in the upper GI tract: preliminary clinical experiences with Wallstents. *Am J Gastroenterol* 1994;**89**:1496–500.

204. Law S, Tung PH, Chu KM, Wong J. Self-expanding metallic stents for palliation of recurrent malignant esophageal obstruction after subtotal esophagectomy for cancer. *Gastrointest Endosc* 1999;**50**:427–36.

205. Laasch HU, Nicholson DA, Kay CL, Attwood S, Bancewicz J. The clinical effectiveness of the Gianturco oesophageal stent in malignant oesophageal obstruction. *Clin Radiol* 1998; **53**:666–72.

206. Spinelli P, Cerrai FG, Ciuffi M, Ignomirelli O, Meroni E, Pizzetti P. Endoscopic stent placement for cancer of the lower esophagus and gastric cardia. *Gastrointest Endosc* 1994;**40**:455–7.

207. Golder M, Tekkis PP, Kennedy C, Lath S, Toye R, Steger AC. Chest pain following oesophageal

stenting for malignant dysphagia. *Clin Radiol* 2001;**56**:202–5.

208. Ell C, May A, Hahn EG. Gianturco-Z stents in the palliative treatment of malignant esophageal obstruction and esophagotracheal fistulas [published erratum appears in *Endoscopy* 1995; **27**:714]. *Endoscopy* 1995;**27**:495–500.

209. Cook TA, Dehn TC. Use of covered expandable metal stents in the treatment of oesophageal carcinoma and tracheo-oesophageal fistula. *Br J Surg* 1996;**83**:1417–18.

210. Kozarek RA, Raltz S, Brugge WR, Schapiro RH, Waxman I, Boyce HW, *et al*. Prospective multicenter trial of esophageal Z-stent placement for malignant dysphagia and tracheoesophageal fistula [published erratum appears in *Gastrointest Endosc* 1996;**44**:764]. *Gastrointest Endosc* 1996; **44**:562–7.

211. Watkinson A, Ellul J, Entwisle K, Farrugia M, Mason R, Adam A. Plastic-covered metallic endoprostheses in the management of oesophageal perforation in patients with oesophageal carcinoma. *Clin Radiol* 1995;**50**:304–9.

212. Bethge N, Sommer A, Vakil N. A prospective trial of self-expanding metal stents in the palliation of malignant esophageal strictures near the upper esophageal sphincter. *Gastrointest Endosc* 1997; **45**:300–3.

213. Conio M, Caroli-Bosc F, Demarquay JF, Sorbi D, Maes B, Delmont J, *et al*. Self-expanding metal stents in the palliation of neoplasms of the cervical esophagus. *Hepatogastroenterol* 1999;**46**:272–7.

214. Macdonald S, Edwards RD, Moss JG. Patient tolerance of cervical esophageal metallic stents. *J Vasc Interv Radiol* 2000;**11**:891–8.

215. Mayoral W, Fleischer D, Salcedo J, Roy P, Al-Kawas F, Benjamin S. Nonmalignant obstruction is a common problem with metal stents in the treatment of esophageal cancer. *Gastrointest Endosc* 2000;**51**:556–9.

216. Neuhaus H, Hoffmann W, Dittler HJ, Niedermeyer HP, Classen M. Implantation of self-expanding esophageal metal stents for palliation of malignant dysphagia. *Endoscopy* 1992;**24**:405–10.

217. Kozarek RA, Raltz S, Marcon N, Kortan P, Haber G, Lightdale C, *et al*. Use of the 25 mm flanged esophageal Z stent for malignant dysphagia: a prospective multicenter trial. *Gastrointest Endosc* 1997;**46**:156–60.

218. Hills KS, Chopra KB, Pal A, Westaby D. Self-expanding metal oesophageal endoprostheses, covered and uncovered: a review of 30 cases. *Eur J Gastroenterol Hepatol* 1998;**10**:371–4.

219. Raijman I, Siddique I, Ajani J, Lynch P. Palliation of malignant dysphagia and fistulae with coated expandable metal stents: experience with 101 patients. *Gastrointest Endosc* 1998;**48**:172–9.

220. Cwikiel W, Stridbeck H, Tranberg KG, von Holstein CS, Hambraeus G, Lillo-Gil R, *et al*. Malignant esophageal strictures: treatment with a self-expanding nitinol stent. *Radiology* 1993; **187**:661–5.

221. Dorta G, Binek J, Blum AL, Buhler H, Felley CP, Koelz HR, *et al*. Comparison between esophageal Wallstent and Ultraflex stents in the treatment of malignant stenoses of the esophagus and cardia. *Endoscopy* 1997;**29**:149–54.

222. Conio M, Gostout CJ. Photodynamic therapy for the treatment of tumor ingrowth in expandable esophageal stents. *Gastrointest Endosc* 1998; **48**:225.

223. Tranberg KG, Stael von Holstein C, Ivancev K, Cwikiel W, Lunderquist A. The YAG laser and Wallstent endoprosthesis for palliation of cancer in the esophagus or gastric cardia. *Hepatogastroenterology* 1995;**42**:139–44.

224. Nelson DB, Axelrad AM, Fleischer DE, Kozarek RA, Silvis SE, Freeman ML, *et al*. Silicone-covered Wallstent prototypes for palliation of malignant esophageal obstruction and digestive–respiratory fistulas. *Gastrointest Endosc* 1997;**45**:31–7.

225. Nelson D, Borowsky S, Murdoch M. Risk of self-expanding metal stents in patients with prior radiation or chemotherapy [letter; comment]. *Gastrointest Endosc* 1999;**49**:137–9.

226. Siersema P, Dees J, van Blankenstein M. Palliation of malignant dysphagia from oesophageal cancer. *Scand J Gastroenterol* 1998;**225** (Suppl):75–84.

227. Maier A, Pinter H, Friehs GB, Renner H, Smolle-Juttner FM. Self-expandable coated stent after intraluminal treatment of esophageal cancer: a risky procedure? *Ann Thorac Surg* 1999; **67**:781–4.

228. Vakil N, Bethge N. Plastic stents in the esophagus: is homemade really better? *Am J Gastroenterol* 1999;**94**:1701–2.

229. Ludwig D, Dehne A, Burmester E, Wiedemann GJ, Stange EF. Treatment of unresectable carcinoma of the esophagus or the gastroesophageal junction by mesh stents with or without radiochemotherapy. *Int J Oncol* 1998;**13**:583–8.

230. Kozarek RA. Esophageal stenting – when should metal replace plastic? [editorial; comment]. *Endoscopy* 1998;**30**:575–7.

231. Kozarek RA. Complications and lessons learned from 10 years of expandable gastrointestinal prostheses [review]. *Dig Dis* 1999;**17**:14–22.

232. Cwikiel W, Tranberg KG, Cwikiel M, Lillo-Gil R. Malignant dysphagia: palliation with esophageal stents – long-term results in 100 patients. *Radiology* 1998;**207**:513–18.

233. Dougenis D, Petsas T, Bouboulis N, Leukaditou C, Vagenas C, Kardamakis D, *et al*. Management of non resectable malignant esophageal stricture and fistula. *Eur J Cardiothorac Surg* 1997;**11**: 38–45.

234. Grund KE, Storek D, Becker HD. Highly flexible self-expanding meshed metal stents for palliation of malignant esophagogastric obstruction. *Endoscopy* 1995;**27**:486–94.

235. Lagattolla NR, Rowe PH, Anderson H, Dunk AA. Restenting malignant oesophageal strictures. *Br J Surg* 1998;**85**:261–3.

236. O'Sullivan GJ, Grundy A. Palliation of malignant dysphagia with expanding metallic stents. *J Vas Interv Radiol* 1999;**10**:346–51.

237. Raltz SL, Kozarek RA. Do age, gender, or tumor location affect outcomes when using metallic stents in the palliative treatment of esophageal carcinoma? *Gastroenterology Nursing* 1999; **22**:249–53.

238. Saxon RR, Morrison KE, Lakin PC, Petersen BD, Barton RE, Katon RM, *et al*. Malignant esophageal obstruction and esophagorespiratory fistula: palliation with a polyethylene-covered Z-stent. *Radiology* 1997;**202**:349–54.

239. Haringsma J, Ferwerda J, Dekker W, Brom HL. Preliminary experience with a new ultraviolet-cured expandable plastic endoprosthesis in the management of malignant esophageal strictures. *Endoscopy* 1997;**29**:188–91.

240. Takimoto Y, Nakamura T, Yamamoto Y, Kiyotani T, Teramachi M, Shimizu Y. The experimental replacement of a cervical esophageal segment with an artificial prosthesis with the use of collagen matrix and a silicone stent. *J Thorac Cardiovasc Surg* 1998;**116**:98–106.

241. Farndon MA, Wayman J, Clague MB, Griffin SM. Cost-effectiveness in the management of patients with oesophageal cancer. *Br J Surg* 1998;**85**:1394–8.

242. McWhinney IR, Bass MJ, Donner A. Evaluation of a palliative care service: problems and pitfalls. *BMJ* 1994;**309**:1340–2.

243. Hudson P, Aranda S, McMurray N. Randomized controlled trials in palliative care: overcoming the obstacles. *Int J Palliat Nurs* 2001;**7**:427–34.

244. Carter R, Smith JS, Anderson JR. Laser recanalization versus endoscopic intubation in the palliation of malignant dysphagia: a randomized prospective study. *Br J Surg* 1992;**79**:1167–70.

245. Roseveare CD, Patel P, Simmonds N, Goggin PM, Kimble J, Shepherd HA. Metal stents improve dysphagia, nutrition and survival in malignant oesophageal stenosis: a randomized controlled trial comparing modified Gianturco Z-stents with plastic Atkinson tubes. *Eur J Gastroenterol Hepatol* 1998;**10**:653–7.

246. Nicholson DA, Haycox A, Kay CL, Rate A, Attwood S, Bancewicz J. The cost effectiveness of metal oesophageal stenting in malignant disease compared with conventional therapy. *Clin Radiol* 1999;**54**:212–15.

247. Watson A. Self-expanding metal oesophageal endoprostheses: which is best? [comment]. *Eur J Gastroenterol Hepatol* 1998;**10**:363–5.

248. Siersema PD, Hop WC, Dees J, Tilanus HW, van Blankenstein M. Coated self-expanding metal stents versus latex prostheses for esophagogastric cancer with special reference to prior radiation and chemotherapy: a controlled, prospective study. *Gastrointest Endosc* 1998;**47**:113–20.

249. O'Donnell CA, Fullarton GM, Watt E, Lennon K, Murray GD, Moss JG. Randomized clinical trial comparing self-expanding metallic stents with plastic endoprostheses in the palliation of oesophageal cancer. *Br J Surg* 2002;**89**:985–92.

250. Taal BG, Kooyman WM, Boot H. Expandable stents compared to conventional plastic endoprostheses in malignant oesophageal obstruction, especially in cardiac cancer and fistulas: the experience of the Netherlands Cancer Institute. *Eur J Gastroenterol Hepatol* 1998; **10**:745–52.

251. Adam A, Ellul J, Watkinson AF, Tan BS, Morgan RA, Saunders MP, *et al*. Palliation of inoperable esophageal carcinoma: a prospective randomized trial of laser therapy and stent placement. *Radiology* 1997;**202**:344–8.

252. Gevers AM, Macken E, Hiele M, Rutgeerts P. A comparison of laser therapy, plastic stents, and expandable metal stents for palliation of malignant dysphagia in patients without a fistula. *Gastrointest Endosc* 1998;**48**:383–8.

253. Vakil N, Morris AI, Marcon N, Segalin A, Peracchia A, Bethge N, *et al*. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. *Am J Gastroenterol* 2001;**96**:1791–6.

254. Siersema PD, Hop WC, van Blankenstein M, van Tilburg AJ, Bac DJ, Homs MY, *et al*. A comparison of 3 types of covered metal stents for the palliation of patients with dysphagia caused by esophagogastric carcinoma: a prospective, randomized study. *Gastrointest Endosc* 2001; **54**:145–53.

255. Buset M, des Marez B, Baize M, Bourgeois N, de Boelpaepe C, de Toeuf J, *et al*. Palliative

endoscopic management of obstructive esophagogastric cancer: laser or prosthesis? *Gastrointest Endosc* 1987;**33**:357–61.

256. Alderson D, Wright PD. Laser recanalization versus endoscopic intubation in the palliation of malignant dysphagia. *Br J Surg* 1990;**77**: 1151–3.

257. Sculpher MJ, Sargeant IR, Loizou LA, Thorpe SM, Spencer GM, Bown SG. A cost analysis of Nd:YAG laser ablation versus endoscopic intubation for the palliation of malignant dysphagia. *Eur J Cancer* 1995;**31A**: 1640–6.

258. Anand BS, Saeed ZA, Michaletz PA, Winchester CB, Doherty MA, Liem JH, *et al*. A randomized comparison of dilatation alone versus dilatation plus laser in patients receiving chemotherapy and external beam radiation for esophageal carcinoma. *Dig Dis Sci* 1998; **43**:2255–60.

259. Carazzone A, Bonavina L, Segalin A, Ceriani C, Peracchia A. Endoscopic palliation of oesophageal cancer: results of a prospective comparison of Nd:YAG laser and ethanol injection. *Eur J Surg* 1999;**165**:351–6.

260. Angelini G, Pasini AF, Ederle A, Castagnini A, Talamini G, Bulighin G. Nd:YAG laser versus polidocanol injection for palliation of esophageal malignancy: a prospective, randomized study. *Gastrointest Endosc* 1991;**37**:607–10.

261. Konigsrainer A, Riedmann B, De Vries A, Ofner D, Spechtenhauser B, Aigner F, *et al*. Expandable metal stents versus laser combined with radiotherapy for palliation of unresectable esophageal cancer: a prospective randomized trial. *Hepatogastroenterol* 2000;**47**:724–7.

262. Sander R, Hagenmueller F, Sander C, Riess G, Classen M. Laser versus laser plus afterloading with iridium-192 in the palliative treatment of malignant stenosis of the esophagus: a prospective, randomized, and controlled study. *Gastrointest Endosc* 1991;**37**:433–40.

263. Sargeant IR, Tobias JS, Blackman G, Thorpe S, Glover JR, Bown SG. Radiotherapy enhances laser palliation of malignant dysphagia: a randomised study. *Gut* 1997;**40**:362–9.

264. Spencer GM, Thorpe SM, Sargeant IR, Blackman GM, Solano J, Tobias JS, *et al*. Laser and brachytherapy in the palliation of adenocarcinoma of the oesophagus and cardia. *Gut* 1996; **39**:726–31.

265. Angorn IB, Haffejee AA. Pulsion intubation v. restrosternal gastric bypass for palliation of unresectable carcinoma of the upper thoracic oesophagus. *Br J Surg* 1983;**70**:335–8.

266. Cantero R, Torres AJ, Hernando F, Gallego J, Lezana A, Suarez A, *et al*. Palliative treatment of esophageal cancer: self-expanding metal stents versus Postlethwait technique. *Hepatogastroenterology* 1999;**46**:971–6.

267. Birch JF, White SA, Berry DP, Veitch PS. A cost–benefit comparison of self-expanding metal stents and Atkinson tubes for the palliation of obstructing esophageal tumors. *Dis Esophagus* 1998;**11**:172–6.

268. Clark A, Fallowfield LJ. Quality of life measurements in patients with malignant disease: a review. *J R Soc Med* 1986;**79**:165–9.

269. Goligher JC. Judging the quality of life after surgical operations. *Journal of Chronic Diseases* 1987;**40**:631–3.

270. Gelfand GA, Finley RJ. Quality of life with carcinoma of the esophagus [review]. *World J Surg* 1994;**18**:399–405.

271. McNeil BJ, Weichselbaum R, Pauker SG. Fallacy of the five-year survival in lung cancer. *N Engl J Med* 1978;**299**:1397–401.

272. Blazeby JM, Williams MH, Alderson D, Farndon JR. Observer variation in assessment of quality of life in patients with oesophageal cancer. *Br J Surg* 1995;**82**:1200–3.

273. Schipper H, Clinch J, Powell V. Definitions and conceptual issues. In Spilker B, editor. *Quality of life assessments in clinical trials*. New York: Raven Press; 1990. pp. 11–24.

274. Griffin SM, Robertson CS. Non-surgical treatment of cancer of the oesophagus [editorial]. *Br J Surg* 1993;**80**:412–13.

275. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. *Health Technol Assess* 1998; **2**(14):i–iv, 1–74.

276. Karnofsky DA, Abalmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1948;**1**:634–56.

277. Hutchinson TA, Boyd NF, Feinstein AR. Scientific problems in clinical scales as demonstrated in KPS. *Journal Chronic Disease* 1979;**32**:661–6.

278. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;**45**:2220–4.

279. Spitzer WO, Dobson AJ, Chesterman E, Levi J, Shepherd R, Battista RE, *et al*. Measuring the quality of life of cancer patients. *Journal Chronic Diseases* 1981;**34**:585–97.

280. Brooks R. EuroQol: the current state of play [review]. *Health Policy* 1996;**37**:53–72.

281. Anonymous. EuroQol – a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;**16**: 199–208.

282. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *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 Nat Cancer Inst* 1993;**85**:365–76.

283. Stoller JL, Samer KJ, Toppin DI, Flores AD. Carcinoma of the esophagus: a new proposal for the evaluation of treatment. *Can J Surg* 1977; **20**:454–9.

284. Brunelli C, Mosconi P, Boeri P, Gangeri L, Pizzetti P, Cerrai F, *et al*. Evaluation of quality of life in patients with malignant dysphagia. *Tumori* 2000;**86**:134–8.

285. Loizou LA, Rampton D, Atkinson M, Robertson C, Bown SG. A prospective assessment of quality of life after endoscopic intubation and laser therapy for malignant dysphagia. *Cancer* 1992;**70**: 386–91.

286. Blazeby JM, Alderson D, Winstone K, Steyn R, Hammerlid E, Arraras J, *et al*. Development of an EORTC questionnaire module to be used in quality of life assessment for patients with oesophageal cancer. The EORTC Quality of Life Study Group. *Eur J Cancer* 1996;**32A**: 1912–7.

287. van Knippenberg FC, Out JJ, Tilanus HW, Mud HJ, Hop WC, Verhage F. Quality of life in patients with resected oesophageal cancer. *Soc Sci Med* 1992;**35**:139–45.

288. McLarty AJ, Deschamps C, Trastek VF, Allen MS, Pairolero PC, Harmsen WS. Esophageal resection for cancer of the esophagus: long-term function and quality of life. *Ann Thorac Surg* 1997;**63**:1568–72.

289. Zieren HU, Jacobi CA, Zieren J, Muller JM. Quality of life following resection of oesophageal carcinoma. *Br J Surg* 1996;**83**:1772–5.

290. Sneeuw KC, Aaronson NK, Sprangers MA, Detmar SB, Wever LD, Schornagel JH. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. *J Clin Epidemiol* 1998;**51**:617–31.

291. McQuay H, Moore A. Need for rigorous assessment of palliative care. *BMJ* 1994; **309**:1315–16.

292. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**: 275–83.

293. Torrance GW. Measurement of health state utilities for economic appraisal [review]. *Journal of Health Economics* 1986;**5**:1–30.

294. Stiggelbout AM, Kiebert GM, Kievit J, Leer JW, Habbema JD, De Haes JC. The 'utility' of the time trade-off method in cancer patients: feasibility and proportional trade-off. *J Clin Epidemiol* 1995; **48**:1207–14.

295. de Haes JC, Stiggelbout AM. Assessment of values, utilities and preferences in cancer patients [review]. *Cancer Treat Rev* 1996;**22** (Suppl A):13–26.

296. van der Donk J, Levendag PC, Kuijpers AJ, Roest FH, Habbema JD, Meeuwis CA, *et al*. Patient participation in clinical decision-making for treatment of T3 laryngeal cancer: a comparison of state and process utilities. *J Clin Oncol* 1995; **13**:2369–78.

297. Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. Whose utilities for decision analysis? *Med Decis Making* 1990; **10**:58–67.

298. Sackett DL, Torrance GW. The utility of different health states as perceived by the general public. *Journal of Chronic Diseases* 1978;**31**:697–704.

299. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998;**85**:1457–9.

300. Department of Health. *NHS Reference Costs*. London: Department of Health; 2001.

301. Dolan P. *A social tariff for EuroQol: results from a UK general population survey*. Discussion Paper 138. Centre for Health Economics; 1995.

302. Lamb P, Dresner S, Shenfine J, Davies S, Hayes N, Griffin S. Palliation of oesophageal carcinoma: a 10-year audit of clinical practice [abstract]. *Gut* 2001;**48** (Suppl I):A23–A31.

303. Wayman J, Forman D, Griffin SM. Monitoring the changing pattern of esophago-gastric cancer: data from a UK regional cancer registry. *Cancer Causes Control* 2001;**12**:943–9.

304. Llewellyn-Thomas HA, Thiel EC, McGreal MJ. Cancer patients' evaluations of their current health states: the influences of expectations, comparisons, actual health status, and mood. *Med Decis Making* 1992;**12**:115–22.

305. Jansen SJ, Stiggelbout AM, Wakker PP, Vliet Vlieland TP, Leer JW, Nooy MA, *et al*. Patients' utilities for cancer treatments: a study of the chained procedure for the standard gamble and time tradeoff. *Med Dec Making* 1998;**18**: 391–9.

306. Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of

metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993;**25**:207–12.

307. Dallal HJ, Smith GD, Grieve DC, Ghosh S, Penman ID, Palmer KR. A randomized trial of thermal ablative therapy versus expandable metal stents in the palliative treatment of patients with esophageal carcinoma. *Gastrointest Endosc* 2001; **54**:549–57.

308. Hanita M. Self-report measures of patient utility: should we trust them? [review]. *J Clin Epidemiol* 2000;**53**:469–76.

309. Miller AR, Cantor SB, Peoples GE, Pearlstone DB, Skibber JM. Quality of life and cost effectiveness analysis of therapy for locally recurrent rectal cancer. *Dis Colon Rectum* 2000;**43**:1695–701; Discussion 1701–3.

310. Sprangers MA, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC Quality of Life Study Group. *Qual Life Res* 1998; **7**:291–300.

Appendix 1

Utility assessment scenarios

Health scenarios

Good health

- You lead an active life and find work and other interests/activities rewarding
- You have good relations with family and friends
- You have a healthy lifestyle in terms of diet and leisure activities
- You have a positive approach to life and rarely feel anxious or depressed
- You have no health problems which cause pain or discomfort
- You welcome new challenges and feel optimistic about the future in both work and personal life

Health scenario 1

- You can eat all sorts of raw and cooked foods
- You eat your usual amount of food
- You do not have any problems carrying out your usual daily activities
- You may have 1 of the following symptoms: pain, shortness of breath

Health scenario 2

- You find it difficult to eat hard solid foods
- You eat less
- You have some problems carrying out your usual daily activities
- You may have 1 or more of the following symptoms: pain, shortness of breath, vomiting & regurgitation

Health scenario 3

- You cannot eat any solid foods
- You eat a lot less
- You have frequent problems carrying out your usual daily activities
- You will have 2 or more of the following symptoms: pain, shortness of breath, vomiting & regurgitation, weak/sore muscles, loss of taste, bad breath

Health scenario 4

- You are limited to a completely liquid diet
- You are not able to eat or drink much before feeling full
- You have a lot of problems carrying out your usual daily activities
- You will have 3 or more of the following symptoms: pain, shortness of breath, vomiting & regurgitation, weak/sore muscles, loss of taste, bad breath, dry mouth

Health scenario 5

- You cannot swallow at all
- You are not able to eat or drink anything
- You are not able to carry out your usual daily activities
- You will have 4 or more of the following symptoms: pain, shortness of breath, vomiting & regurgitation, weak/sore muscles, loss of taste, bad breath, dry mouth, drooling saliva, persistent cough & wheeze

Treatment scenarios

Treatment scenario 1

- You have frequent problems carrying out your usual daily activities (these may include visiting friends/family, housework, leisure activities, going out for meals)

You are about to receive treatment which involves:

- Making 1 trip to hospital
- Being admitted to hospital for 2 nights
- Having moderate pain for a few days after treatment

After treatment you are less likely to have problems carrying out your usual daily activities

Treatment scenario 2 (identical to treatment scenario 1 apart from the following)

- Making 1 trip to hospital
- Not being admitted to hospital
- Having moderate pain for 2 weeks after treatment

Treatment scenario 3 (identical to treatment scenario 1 apart from the following)

- Making 2 or 3 trips to hospital
- Being admitted into hospital for 1 night on each trip
- Having mild pain for a few days after each treatment

Appendix 2

Unit cost table: procedures

Procedures	Mean cost (£)
Upper gastrointestinal endoscopy	
Diagnostic	150
Removal of foreign body	300
Endoscopy + dilatation	300
Insertion of rigid oesophageal endoprosthesis	350
Insertion of self-expanding metal stent	1200
Repositioning of oesophageal prosthesis	300
Argon plasma coagulation/laser treatment	350
Injection of ethanol into tumour	320
BICAP	350
Insertion of fine bore feeding tube	300
Percutaneous endoscopic gastrostomy	400
Percutaneous endoscopic jejunostomy	350
Diagnostic bronchoscopy	298
Radiotherapy	
Brachytherapy to oesophagus: selectron/microselectron	1112
Palliative external beam to oesophagus	437
Palliative external beam to other sites:	122
Shoulder	122
Ribs	122
Hip	122
Radiology	
X-ray:	17
Chest	17
Abdomen	36
Thoracic spine	17
Hip	36
Lumbar spine	17
Femur	36
Cervical spine	17
Foot	104
Contrast swallow (water-soluble and barium sulfate)	130
Computed tomography:	130
Thorax	109
Abdomen	130
Head	67
Thorax and abdomen	245
Abdominal ultrasound scan	
Ventilation–perfusion scan	
Other	
Pleural tap	20
Insertion of intercostal chest drain	50
Examination under anaesthesia: rectum	330
ECG	40
Blood transfusion	80
Transfusion of fresh-frozen plasma	30
Echocardiogram	50

Appendix 3

Cost table: hospital attendance

Hospital attendance	Mean cost (£)
Inpatient (per ward per overnight stay)	
Surgical	197
Otorhinolaryngology (ENT)	192
Medical	137
Elderly care	136
Oncology	160
Orthopaedic	170
Ophthalmology	269
Surgical high-dependency unit	459
Outpatient (per attendance)	
Radiotherapy unit	87
Endoscopy day unit	80
Casualty attendance	57
Haematology day unit	
First attendance	90
Subsequent attendance	58

Appendix 4
CONSORT table

Assessment			
Assessed for eligibility	695		
Exclusions			
Excluded:	478		
Not meeting inclusion criteria	437		
Refused to participate	27		
Other	14		
Randomisation			
Randomised	217		
Allocation			
SEMS		*Non-SEMS*	
Allocated to SEMS	108	Allocated to non-SEMS	109
Received SEMS	102	Received non-SEMS	98
Did not receive SEMS	6	Did not receive non-SEMS	11
Reasons for not receiving allocated treatment:			
Inappropriate randomisation	0	Inappropriate randomisation	6
Double randomisation	0	Double randomisation	1
Treatment not required	2	Treatment not required	1
Immediate withdrawal	2	Immediate withdrawal	2
Other treatment given	2	Other treatment given	1
Lost to follow-up	1	Lost to follow-up	0
Analysis			
SEMS		*Non-SEMS*	
Analysed	104	Analysed	99
Excluded from analysis	4	Excluded from analysis	11
Reasons for exclusion:			
Treatment not required	2	Treatment not required	1
Immediate withdrawal	2	Immediate withdrawal	2
Inappropriate randomisation	0	Inappropriate randomisation	6
Double randomisation	0	Double randomisation	1

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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