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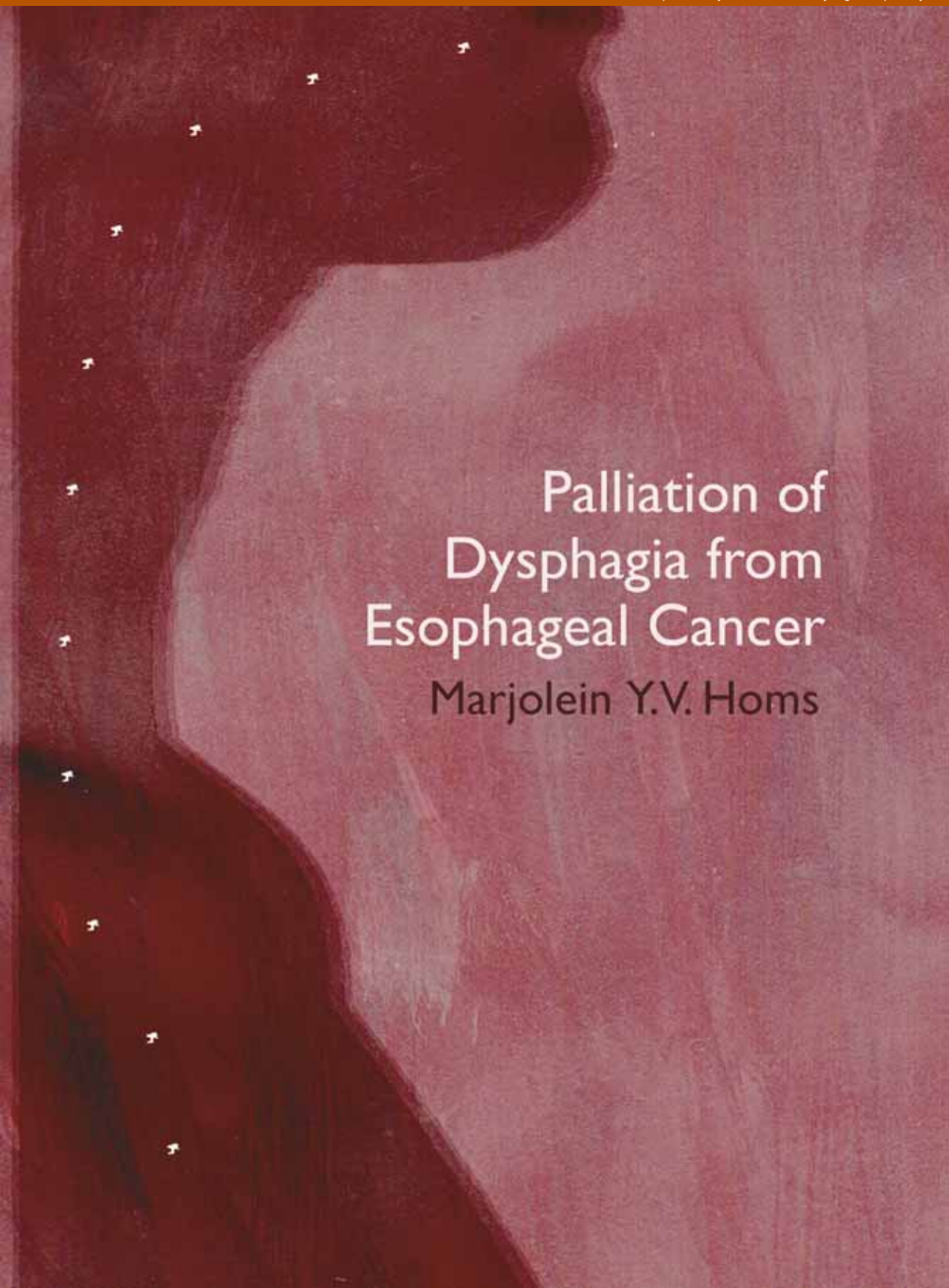

Palliation of Dysphagia from Esophageal Cancer

Marjolein Y.V. Homs

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Palliatie van voedselpassageklachten ten gevolge van slokdarmkanker

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I feel that the greatest reward for doing
is the opportunity to do more
Jonas Salk

CONTENTS

1

General introduction and objectives

In the Netherlands, on average 1100 new patients are diagnosed annually with esophageal cancer. The prognosis of esophageal cancer is poor with a 5-year survival of 10-15% (1, 2). A surgical resection is currently the primary treatment for esophageal cancer if a patient is fit enough to undergo surgery and the tumor is considered resectable without evidence of distant metastases. More than 50% of patients with esophageal cancer have an inoperable disease at presentation due to locally advanced or metastatic disease, or severe co-morbidity. For these patients restoration of the ability to eat is the only possible therapy. Since most of these patients live no longer than 6 months, the aim of palliative treatment is to relieve dysphagia rapidly with minimal or no hospital stay and to maintain the ability to swallow during life thus improving or maintaining quality of life.

Treatment options most commonly used for palliation of malignant dysphagia include self-expanding metal stent placement (3-7), laser therapy (8, 9), external beam radiation in combination with brachytherapy (10, 11), and brachytherapy as a single treatment (12-15). A disadvantage of laser therapy is that repeated treatment sessions are required to achieve and maintain adequate palliation (8, 9). A combined treatment of external beam radiation with brachytherapy is often too intensive for patients with metastatic disease and a poor medical condition. Therefore, in many patients with inoperable disease, placement of a self-expanding metal stent or single dose brachytherapy are used for the palliation of dysphagia (16). Both these treatment modalities have been proven to be effective in relieving dysphagia with a low complication rate (4-7, 12-15), however, their relative effectiveness is unknown.

A self-expanding metal stent is a flexible tube made of a metal mesh with a plastic coating. This stent can be inserted into the esophagus during an endoscopic procedure to restore a normal food passage to the stomach. The stent can be deployed through the stenosis and will gradually expand within 24 hours after placement. Several types of metal stents are available, of which the Ultraflex stent, the Flamingo Wall stent and the Z-stent are most commonly used. These 3 types of stents were compared in a randomized study with 100 patients in our hospital. No major differences existed in effectiveness, occurrence of complications and recurrent dysphagia between these stents (4). We therefore decided to use the Ultraflex stent as this stent is most commonly used worldwide.
Brachytherapy (intraluminal radiotherapy) is a local intraluminal radiation. During endoscopy a guide wire is left, over which a flexible applicator with a radioactive source is passed down the esophagus. A radiation dose between 7.5-20 Gy can be

administered to the esophageal tumor in 1 to 3 treatment sessions. A major advantage of single dose brachytherapy in comparison to external beam radiation is the ability to deliver a maximum radiation dose directly to the tumor without damaging the healthy surrounding tissue. Based on the literature (12) and the experience of radiotherapists we decided to use a single dose of 12 Gy brachytherapy.

Both treatments (stent placement and single dose brachytherapy) are frequently used in the Netherlands for the palliation of dysphagia of esophageal carcinoma, however, these treatments have never been compared in a randomized trial. In addition, a longitudinal extensive investigation of health related quality of life after these palliative treatments has never been performed. Also, treatment costs and total medical costs are important outcome measures because of the high initial costs of metal stents.

Objectives of this thesis:

Primary objective

- To compare stent placement and single dose brachytherapy with respect to relief of dysphagia, complications, treatment for persistent or recurrent dysphagia, health related quality of life, and costs.

Secondary objectives

- To survey the diagnostic procedures and treatment strategies currently employed in hospitals for patients with esophageal carcinoma.
- To evaluate the outcome of single dose brachytherapy performed in a 10 year-period in our hospital.
- To investigate specific stent related problems, including the influence of prior treatment with radiation and/or chemotherapy on the outcome of stent placement and occurrence and causes of recurrent dysphagia after stent placement and the outcome of re-intervention for recurrent dysphagia.
- To evaluate the outcome of a new type of metal stent to prevent gastro-esophageal reflux.

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2

Palliative treatment of esophageal carcinoma

Based on:
Chapter 30: Endoscopic palliation for malignant dysphagia and esophageal fistulae

M.Y.V. Homs, P.D. Siersema

Clinical Gastrointestinal Endoscopy

2.1 INTRODUCTION

Annually, cancer of the esophagus and gastro-esophageal junction is diagnosed worldwide in more than 400,000 patients, which makes it the 8th most common malignancy and 6th on the list of cancer mortality causes (1). It is somewhat difficult to determine its true incidence, since cancer of the gastro-esophageal junction is sometimes classified as gastric cancer and sometimes as esophageal cancer. In clinical practice, this distinction is not very important since for both cancer of the esophagus and cancer of the gastro-esophageal junction, the curative and palliative options for treatment are the same.
Cancer of the esophagus and gastro-esophageal junction carries a poor prognosis with a 5-year survival rate of 10-15% (2). This is partly due to the fact that more than 50% of patients with carcinoma of the esophagus or gastro-esophageal junction have already inoperable disease at presentation. Most of these patients require palliative treatment to relieve progressive dysphagia.

This chapter will focus on the epidemiology and pathogenesis of inoperable cancer of the esophagus and gastro-esophageal junction. The two most commonly used methods for palliation of dysphagia due to inoperable cancer of the esophagus, namely single dose brachytherapy and stent placement, will be discussed.

2.2 EPIDEMIOLOGY

Squamous cell carcinoma

The incidence of squamous cell carcinoma varies from country to country, and also within a country it may be more often detected in certain regions. About two-third of new cases of squamous cell carcinoma are detected in China (47%) and Central Asia (19%). This is called the 'Central Asia Esophageal Cancer Belt'. The incidence of squamous cell carcinoma in this area varies from 19 per 100,000 in Azerbaijan to 340 per 100,000 in the northern part of China. The incidence of squamous cell carcinoma in Western Europe and the USA is much lower, i.e., 3-6 per 100,000. In Western countries, squamous cell carcinoma of the esophagus is mainly found in the older age group with the highest incidence between 50 and 70 years. The distribution between males and females is 3-4 to 1 (3).

Adenocarcinoma

Until about 1970, more than 90% of esophageal cancers were squamous cell carcinomas. However, population based studies have shown a large increase in the

incidence of adenocarcinoma of the esophagus and gastro-esophageal junction over the last 30 years in North America and Western Europe, especially among white males (4, 5). In males, the incidence of adenocarcinoma of the esophagus and gastro-esophageal junction has now surpassed that of squamous cell carcinoma (6). In the USA, the annual rates per 100,000 population for esophageal adenocarcinoma rose from 0.7 during 1974-1976 to 3.2 during 1992-1994, an increase of >350% (5). The same trend, although less rapidly, has been reported in other countries, such as Australia, New Zealand, and in Western Europe (7).

Many believe that the increase in (esophageal) adenocarcinoma is related to an increase in the incidence of Barrett's esophagus. In a report from Scotland, Prach et al. (8) found that the incidence of new diagnoses of Barrett's esophagus increased from 1 per 100,000 in 1980 to 48 per 100,000 in 1992. The rate of Barrett's esophagus detection increased over the same years from 1.4 to 42.7 (16.5 if only cases with histological conformation were included) per 1000 endoscopical procedures.

Multiple reports confirm that adenocarcinoma of the esophagus and gastro-esophageal junction occurs more frequently in white males. The distribution between males and females is 4 to 1. Most patients with esophageal adenocarcinoma are older individuals with a peak incidence around 65 year (9). The world-wide distribution of esophageal cancer (for males) is shown in Figure 1.

2.3 PATHOGENESIS

Squamous cell carcinoma

- Smoking and alcohol. The most important risk factors for squamous cell carcinoma in Western Europe and the USA are smoking and alcohol intake. The squamous cell carcinoma risk is increased by a factor 5 for moderate smokers and a factor 10 for heavy smokers. It has been shown that alcohol intake and smoking are independent risk factors for the development of esophageal squamous cell carcinoma (10).
- Food. In Hong Kong, a correlation has been established between the use of pickled vegetables and the development of squamous cell carcinoma. It was found that this was caused by herbs that were used for these vegetables, which were often contaminated with toxic fungi (11).
- Prior radiation therapy has been associated with an increased squamous cell carcinoma risk. A recent study demonstrated that patients who underwent

radiation therapy for breast cancer more than 10 years ago had an increased risk of developing squamous cell carcinoma in the esophagus (12).

- Hot drinks, particularly tea in certain areas in Asia, are associated with an increased risk of developing squamous cell carcinoma. The suggested mechanism is chronic irritation of the esophageal mucosa caused by these hot drinks (13).
- The role played by human papillomavirus (HPV) is unclear. In South Africa, where the incidence of squamous cell carcinoma is high, HPV DNA was detected in more than 50% of cancers (14). In contrast, in the Netherlands, the presence of HPV in squamous cell carcinoma is rare (15).

Disorders associated with an increased squamous cell carcinoma risk

- Achalasia. In a cohort study from Sweden, in which 1062 patients with achalasia were followed, the risk of squamous cell carcinoma was increased by a factor 16 after a follow-up of 9864 patient-years (16). Since most tumors were detected at an advanced stage, a 'curative' resection was only possible in a minority of the patients.
- Caustic ingestion. The incidence of esophageal squamous cell carcinoma is increased by a factor 1000-3000 in patients with a stricture in the esophagus caused by a caustic ingestion. The risk of developing a malignancy is probably highest after the ingestion of lye (17). The mean time between ingestion of a corrosive agent and the development of squamous cell carcinoma is 30-40 years.
- Head and neck cancer. Squamous cell carcinoma of the esophagus and the (hypo-) pharynx are both associated with smoking and alcohol intake. Therefore, it is not surprising that 1-8% of the patients with head and neck cancer also have esophageal cancer or will develop it at a later stage (18). This means that the risk of esophageal cancer is increased by a factor 3-10 in patients with head and neck cancer.

Adenocarcinoma

- Gastro-esophageal reflux disease. A direct association between reflux and adenocarcinomas rather than the presumed sequence of reflux disease leading to Barrett's esophagus and this condition leading to adenocarcinoma was found by Lagergren et al. (19). The esophageal adenocarcinoma risk was 7.7 times increased in persons with heartburn and acid reflux occurring at least once per week. For those with severe symptoms for 20 years or longer, the risk was 43.5

times increased for esophageal adenocarcinoma, but only 4.4 times increased for adenocarcinoma of the gastric cardia. There was no correlation with squamous cell carcinoma.

- Barrett's esophagus. Barrett's esophagus is a disorder of the distal esophagus, in which the squamous epithelium is replaced by metaplastic columnar epithelium. Barrett's esophagus is a complication of long-standing gastro-esophageal reflux disease (GERD) (20). A causal relationship between Barrett's esophagus and the development of esophageal adenocarcinoma has been established.

  In older reports, the risk of esophageal adenocarcinoma in long segment Barrett's esophagus was 30-52 times greater than that of the normal population. In other words, cancer was diagnosed at a median rate of about 1 per 100 patient-years of follow-up. However, these reports were often based on a short period of follow-up with the possibility of including prevalent cancers as incidence cases and therefore may have overestimated the cancer risk. More recent reports with longer follow-up found one cancer per 180-200 patients-years of follow-up (21). The prevalence of Barrett's esophagus in consecutive patients undergoing endoscopy for any clinical indication varies between 0.3% and 2% (22). Several studies have shown that Barrett's esophagus is a disorder of whites and is mainly found in Western Europe. The distribution between males and females is 2.5-4 to 1 (9).

2.4 TREATMENT

A surgical resection is currently the primary treatment for esophageal cancer if a patient is fit enough to undergo surgery and the tumor is considered resectable without evidence of distant metastases. Resection of the esophagus with a gastric pull-up or a colonic interposition is however an invasive procedure with significant morbidity and mortality, and most patients have recurrent tumor growth within the first few years after treatment (23). Neo-adjuvant chemotherapy or chemoradiation may improve the results of surgery and may prevent patients from recurrent disease (24-26). In the past decade, endoscopic methods have been developed to remove early cancers in the esophagus via a non-surgical endoscopic way.

In patients with inoperable esophageal cancer due to locally advanced or metastatic disease, or severe co-morbidity, restoration of the ability to eat is the only possible therapy. Since most of these patients live no longer than 6 months, the aim of palliative treatment is to relief dysphagia rapidly with minimal or no hospital stay,

to maintain swallowing during life and to avoid serious complications. It is important to realize that treatment of incurable esophageal cancer should be individualized and based on tumor stage, medical condition and performance status of the patient, and the patient's personal wishes. In addition, both the available expertise and equipment, and the results of prospective, randomized studies should be taken into consideration.

There is a wide variety of palliative techniques currently available (Table 1). Treatment options most commonly used for palliation of dysphagia include self-expanding metal stent placement (27-31), laser therapy (32, 33), external beam radiation in combination with brachytherapy (34, 35), and brachytherapy as a single treatment (36-39). A disadvantage of laser therapy is that repeated treatment sessions are required to achieve and maintain adequate palliation (32, 33). For patients with extensive local-regional tumor growth and a good clinical condition, a combined treatment of brachytherapy with external beam radiotherapy might result in good local tumor regression and relief of dysphagia (34, 35, 38). The treatment schedule most often used involves a total of 50 Gy external beam radiation delivered in 25 fractions combined with one or two session of brachytherapy (10-15 Gy). This schedule is often too intensive for inoperable patients with metastases or a poor general condition. Therefore, in many patients with inoperable disease, single dose brachytherapy or placement of a self-expanding metal stent are used for the palliation of dysphagia (40).

Palliative chemotherapy may result in local and distant tumor control and possibly also in prolonged survival. Chemotherapy most commonly consists of combination regimes of cisplatin with paclitaxel and/or 5-FU, etoposide or another agent for both squamous cell carcinoma and adenocarcinoma. Response rates (including complete and partial responses) range from 25 to 45% for metastatic disease with acceptable toxicity, however, the effect on survival remains undetermined (41-43). Several new agents and combination of agents are currently under investigation.

Table 1: Palliative modalities for esophageal carcinoma

Modality
Non-Endoscopic techniques
Surgery
Radiation therapy
External beam radiotherapy
Intraluminal radiotherapy (brachytherapy)
Chemotherapy
Endoscopic Techniques
Stent placement
Self-expanding metal stents
Laser therapy
Thermal (Nd:YAG)
Photodynamic therapy
Dilation
Electrocoagulation (BICAP probe)
Chemical Injection Therapy
Nutritional Support
Nasoenteric feeding tube
Percutaneous endoscopic gastrostomy (PEG)

2.5 SINGLE DOSE BRACHYTHERAPY

Since 1980, brachytherapy (intraluminal radiotherapy) in combination with external beam radiation has been used for the treatment of esophageal carcinoma. In 1987, brachytherapy as a single treatment has been introduced for the palliation of dysphagia caused by inoperable esophageal carcinoma due to metastatic disease or a poor medical condition.

In the past, the most commonly used source for brachytherapy was caesium (^{137}Cs), but nowadays, iridium (^{192}Ir) has replaced the heavy caesium. Brachytherapy can be delivered at different dose rates. These are classified as low dose rate (LDR) delivering a dose of 0.4-2 Gy per hour, medium dose rate (MDR) with a dose of >2-12 Gy per hour, and the most recently developed high dose rate (HDR), with a dose of more than 12 Gy per hour. The treatment time is substantially shorter with HDR brachytherapy, resulting in a much more patient-friendly treatment which can be carried out as an outpatient procedure (44).

Single dose brachytherapy is frequently used in Western Europe, South Africa, Japan and to a lesser extent in the USA. To date, ten studies have reported that in the majority of patients dysphagia can effectively be palliated by brachytherapy in doses varying between 7.5 and 20 Gy given in 1-3 treatment sessions (34, 37, 39, 45-53) (Table 2). An advantage of brachytherapy (from the old Greek language meaning from a short distance) in comparison to external beam radiation is the ability to deliver a maximum radiation dose directly to the tumor without damaging the healthy surrounding tissue. In addition, in particular with HDR brachytherapy, time of treatment is short, approximately 20-30 minutes.

2.5.1 Description of brachytherapy procedure

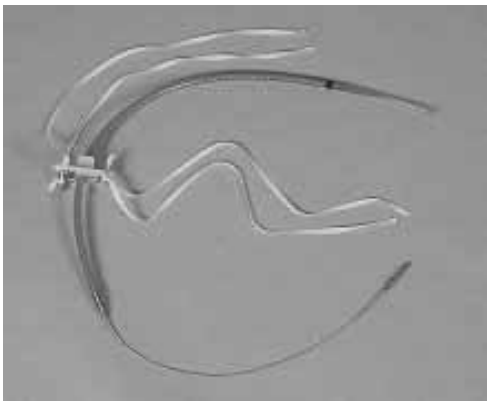
Prior to brachytherapy, an endoscopy is performed. If needed, the stricture is dilated to a maximum of 11 mm by dilation with a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC, USA). The proximal and distal tumor margins are marked by injecting radiographic contrast medium into the submucosa of the esophageal wall through a sclerotherapy needle. Then a guide wire is left. For brachytherapy, a flexible applicator (Bonvoisin-Gérard Esophageal Applicator, Nucletron, Veenendaal, The Netherlands) with a diameter of 10 mm is passed down the esophagus (Figure 2A). In some patients a feeding tube (charrière 14) can be used as applicator for brachytherapy. A thread with 'dummy loads' is introduced into the applicator. A chest X-ray is made, to check the position of the applicator with the 'dummy loads' (Figure 2B). A dose of 7.5-20 Gy is administered with the radioactive source ^{192}Iridium at 1 cm from the source axis of the applicator in 1-3 sessions. In our center, a single dose of 12 Gy is the most commonly used treatment. The dose distributed to the surface of the tumor (5 mm from the source axis) will amount 200% of the prescribed dose. The dose administrated at 12.5 mm from the source axis is then 65% (at 7.5 mm depth inside the tumor). The standard active length of the application is the tumor length plus two centimeters extra at both ends of the tumor. The mean application time of the procedure is 15-20 minutes. It is advisable to prescribe sucralfate (Ulcogant®, E. Merks Nederland, Amsterdam) for a period of 4 weeks after single dose brachytherapy as a prophylactic measure for odynophagia (54).

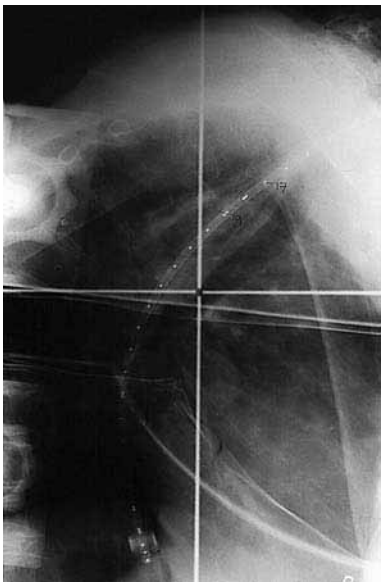
Table 2: Overview of studies using brachytherapy for palliation of patients with an inoperable esophagogastric carcinoma.

Author	N	Dose	Dysphagia Improved	Complications	Recurrent dysphagia	Survival
Giles Rowland et al. 1985 (46)	40	15Gy/1x	65%	12.5% esophagitis	?	?
Low et al. 1992 (51)	12	15Gy/1x	83%	33% esophagitis, 17% pain, 17% pyrexia, 8% bleeding	30%	?
Harvey et al. 1993 (47)	A: 10 B: 12	20Gy/3x 12.5Gy/1x	90% 92%	30% 80% esophagitis	30% 39%	4 months 5.8 months (mean)
Brewster et al. 1995 (37)	197	7.5-20Gy/1x	54%	2% severe complications	?	136 days (median)
Jager et al. 1995 (48)	88	15Gy/1x	67%	34% retrosternal pain, 1% hematemesis, 6% fistulae	37%	5.5 months (median)
Kulhavy et al. 1995 (49)	A:12 B:14 C:14 D:11	10Gy/1x 12Gy/1x 15Gy/1x 18Gy/1x	3/4 8/8 6/6 3/7	0% 0% 0% 9% fistulae	17% 14% 7% 27%	?
Leung et al. 1995 (50)	10	7.1-60Gy/1x	90%	0%	10%	3 months (median)
Sur et al. 1998 (52)	A: 36 B: 68 C: 68	12Gy/2x 16Gy/2x 18Gy/3x	?	14% strictures, 20% fistulae 25% strictures, 3% fistulae 42% strictures, 11% fistulae	?	10%, 1 year 22%, 1 year 35%, 1year
Sur et al. 2002 (39)	A: 112 B: 120	16Gy/2x 18Gy/3x	?	11% strictures, 10% fistulae	12% persistent disease, 35% additional treatment	237 days (median)
Sharma et al. 2002 (53)	58*	6Gy/2x	48%	15% strictures, 10% ulceration, fistulae 5%	?	7 months (median)

*of which 20 patients received a combination of 20-30 Gy external beam radiation and brachytherapy, no separate data were given for the group treated only with brachytherapy.

Figure 2: Esophageal applicator for single dose brachytherapy (left) and chest X-ray before start of the brachytherapy to check the position of the applicator (right).





2.5.2. Complications and recurrent dysphagia

Major complications after single dose brachytherapy mainly consist of fistula formation, hemorrhage, aspiration pneumonia, fever and severe pain. Recurrent dysphagia following single dose brachytherapy is most commonly caused by tumor persistence, tumor recurrence and stricture formation. Minor complications are mainly mild retrosternal pain and radiation esophagitis (Table 2).

Fistula formation

Tumors that infiltrate into surrounding tissue, most commonly the respiratory tract and occasionally the aorta, mediastinum or pleura, are most likely prone to develop a fistula. Patients with evidence of deep ulceration of the tumor or macroscopic growth into the tracheal lumen should therefore be excluded from brachytherapy. Fistula formation has been reported to occur in around 3-10% of patients (Table 2). Treatment of a fistula should be instantly, as fistula formation is a life-threatening complication, which in case of esophagorespiratory fistulas can result in serious pulmonary infection from aspiration pneumonia. Placement of a covered metal stent is the treatment of choice (55-57).

Hemorrhage

Hemorrhage most commonly occurs as a late complication. It is often unsure whether this is due to the treatment or progression of the disease. Hemorrhage after brachytherapy has been reported in up to 5% of patients (Table 2). Treatment consists of blood transfusions, sometimes in combination with a short course of external beam radiotherapy.

Tumor persistence and tumor recurrence

Tumor persistence and tumor recurrence are the most predominant causes of an additional treatment after single dose brachytherapy (Table 2). Reported incidences vary widely between 10-40%. Treatment most commonly consists of a second dose of brachytherapy or placement of a metal stent.

Radiation esophagitis

Radiation esophagitis is a frequently reported early complication after radiation therapy with incidence rates up to 80%. Radiation esophagitis is more commonly observed with high radiation doses or combined external and intraluminal radiotherapy. It is advisable to prescribe prophylactic oral sucralfate for a period of 4 weeks to prevent radiation esophagitis (54). It is thought that sulcralfate coats the mucosa and in that way promotes the healing of radiation induced ulcers and edema (54). In our experience, radiation esophagitis is only a minor problem if single dose brachytherapy with a radiation dose of 12-15 Gy is used in combination with sulcralfate.

2.6 SELF-EXPANDING METAL STENTS

Placement of a self-expanding metal stent is a frequently used method for palliation of malignant dysphagia. Since 1990, more then 75 studies have been published on the outcome of metal stent placement for the palliation of esophageal carcinoma (summarized in (58-60)).

2.6.1 Metal Stents versus Prosthetic Tubes

Metal stents have several advantages over the previously used prosthetic tubes, since they can be inserted with a minimum of dilation, the diameter of the delivery catheters being only 7-11 mm. After placement of a metal stent, the stent expands gradually, which potentially decreases the occurrence of subsequent procedure-

related complications. Moreover, the larger lumen achieved from 16 to 24 mm, and the flexibility of metal stents should improve the quality of swallowing compared to prosthetic tubes. An advantage of prosthetic tubes is the low cost compared to the more expensive metal stents.

Several randomized trials have been performed comparing metal stents with prosthetic tubes (61-66). In summary, these studies have demonstrated that placement of a metal stent is associated with fewer procedure-related complications than a prosthetic tube (62, 63, 65, 66). In one study, metal stents were also more effective in improving dysphagia (64). Studies on cost-effectiveness have shown that, despite the high initial purchase costs, metal stents were more cost-effective than prosthetic tubes because of a shorter hospital stay for procedures for stent-related complications (61, 62, 64, 67).

2.6.2 Currently Available Metal Stents

Special stent characteristics are needed for the effective palliation of tumors of the distal esophagus and the gastric cardia. The ideal stent would have the following characteristics:

- it would have a large internal diameter to ensure the passage of a normal diet;
- it would be flexible and non-traumatic while still achieving full expansion;
- it would not migrate, yet could be repositioned or removed if necessary.

Although this ideal stent does not exist, all available covered metal stents do meet some of these criteria (Table 3).

The Ultraflex stent (Boston Scientific, Natick, Massachusetts, USA) consists of a knitted nitinol wire tube, and the covered version has a polyurethane layer which covers the midsection of the stent extending to within 1.5 cm of either end of the stent (Figure 3). The stent has a proximal flare with two sizes: 28 mm (distal diameter 23 mm) and 23 mm (distal diameter 18 mm). The stent has an easy-to-use delivery system, and can be deployed gradually either from the proximal to the distal end or vice versa. It is important to remember that the degree of shortening after stent placement is 30–40%. The radial force of the Ultraflex stent is the lowest amongst the currently available metal stents. Partial obstruction of the stent may occur in stents that are sharply angulated after crossing the gastro-esophageal junction.

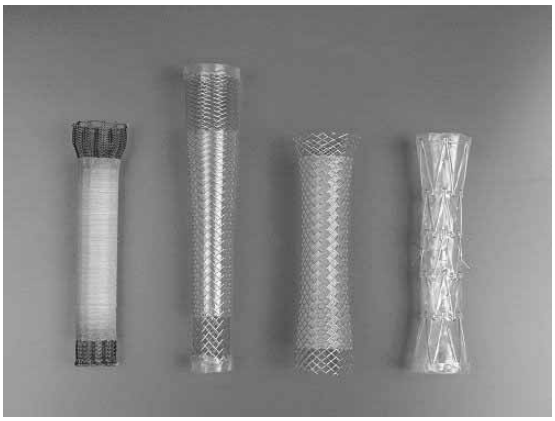
Table 3: Characteristics of the presently available types of metal stents.

Stent type	Covering	Length (cm)	Diameter (mm)	Release system	Radial force	Degree of shortening	Flexibility	Stent material	Manufacturer
Ultraflex	Partial	10, 12, 15	18, 22	Proximal / Distal	Low	30-40%	High	Nitinol	Boston Scientific, Watertown, MA
Wallstent II	Partial	10, 15	20	Distal	High	20-30%	Moderate	Cobalt-based alloy	Boston Scientific, Watertown, MA
Flamingo Wallstent	Partial	12 14	Prox:24/dist:16 Prox:30/dist:20	Distal	High	20-30%	Moderate	Cobalt-based alloy	Boston Scientific, Watertown, MA
Z-stent	Full	6, 8, 10, 12, 14	18, 22 .	Distal	Moderate	None	Low	Stainless steel	Wilson Cook, Winston-Salem, NC
Choo-stent	Full	8, 11, 14, 17	18	Distal	Moderate	None	Low	Nitinol	M.I. Tech, Seoul, Korea

The Wallstent (Boston Scientific) is made from cobalt-based alloy and is formed into a tubular mesh and is available in two designs: the Wallstent II and the Flamingo Wallstent (available only in Europe) (Figure 3). Stents of both designs are easy to place. The Wallstent can be repositioned during the procedure because recapturing remains possible when less than 50% of the stent is expanded. The degree of shortening after placement is about 20-30%. Both designs have a high radial force. The Wallstent II flares to 28 mm at both ends with a diameter of 20 mm at its midsection. It is covered with a silicone polymer layer, with 2 cm left unexposed at the proximal and distal ends. The Flamingo Wallstent is designed specifically for use in the distal esophagus/gastric cardia, however it can be used in the more proximal part of the esophagus as well. This conical shaped stent is designed to apply a variable radial force throughout the length of the stent to address anatomical differences in the distal esophagus and gastric cardia. The stent is covered by a polyurethane layer, which is applied from the inside, extending to within 2 cm of either end of the stent. Both a large-diameter stent (proximal and distal diameters 30 and 20 mm) and a small-diameter stent (proximal and distal diameters 24 and 16 mm) are available. The Wallstent II and the Flamingo Wallstent are both very pliable, with the diameter of the stent being unaffected even when angulated.

The Z-stent (Wilson-Cook Medical, Winston-Salem, North Carolina, USA) with a Korean modification, the Choo stent (M.I. Tech, Seoul, Korea), consists of a wide "Z"-mesh of stainless steel covered over its entire length by a polyethylene layer (Figure 3). The Z-stent is available with (Europe) or without (U.S.A.) fixing barbs in the central segment. The introduction system is more complex than that of the (Flamingo) Wallstent and the Ultraflex stent. The stent does not shorten on release and is the least flexible of the currently available metal stents. The Z-stent flares to 25 mm at both ends with a diameter at its midsection of either 18 mm or 22 mm.

Figure 3: Currently available covered metal stents, from left to right: Ultraflex stent, Flamingo Wallstent, Wallstent II, and Z-stent. The Song stent is not shown, but has a design which is comparable to the Z-stent.



2.6.3 Comparison of different types of metal stents

There are two retrospective studies and two prospective randomized trials comparing the outcome of different types of metal stents. A retrospective study, including 96 patients, compared the uncovered Ultraflex, covered and uncovered versions of the Wallstent, and the covered Z-stent. No differences were found in outcome and complication rate between these stent types (68). Covered versions of the Wallstent and the Ultraflex stent were compared in another retrospective study, showing a higher early complication rate with the Wallstent, but a higher re-intervention rate with the Ultraflex stent (69). In a prospective trial, 100 patients were randomized to one of three types of covered metal stents, the Ultraflex stent, the Flamingo Wallstent, and the Z-stent. There were no significant differences in dysphagia improvement, and the occurrence of complications or recurrent dysphagia, although there was a trend towards more complication with the Z-stent (Ultraflex stent: 8/34 (24%), Flamingo Wallstent: 6/33 (18%) and Z stent: 12/33 (36%); p=0.23) (28). In another prospective trial, the Ultraflex stent and the Flamingo Wallstent were compared in patients with distal esophageal cancer. The two stent types were equally effective in the palliation of dysphagia in this patient group, and the complication rate associated with their use was also comparable (Ultraflex stent: 7/31 (23%) and Flamingo Wallstent: 5/22 (23%)) (70).

From these data, it can be concluded that there are only minor differences between the most commonly used stent types. The choice of stent should therefore be determined by the location and the anatomy of the malignant stricture on the one hand and the specific characteristics of the stent on the other hand (Table 3).

2.6.4 Description of the Stent Placement Procedure

Placement of a metal stent is usually done with the patient under sedation. When fluoroscopy is used, the proximal and distal margins of the stricture are demarcated endoscopically by skin markers, tissue clips, or the intramucosal injection of a radiopaque contrast agent. Injection of the lipid-soluble contrast agent lipiodol results in a persistent mark. Accurate placement of the Ultraflex stent is also possible under endoscopic guidance without the aid of fluoroscopy. This can be done by the application of an external marker at the level of the proximal radiopaque marker on the stent, allowing the stent to be placed under direct endoscopic visualization (71). This technique is at present only feasible with the Ultraflex stent release system. Finally, metal stents can be placed under fluoroscopy guidance alone, without the use of endoscopy (72).
In most institutions, a stenotic malignant stricture is dilated to a diameter of 9–10 mm prior to stent placement, to measure stricture length and to accurately place a guide wire. Dilation may increase the risk of perforation. There is however no consensus on whether one or more dilation sessions preceding stent placement will lower this risk of perforation. The next step is to place a stiff guidewire, for example a 0.038 inch Savary guidewire, across the stricture into the stomach or, preferably, the duodenum and withdraw the endoscope.

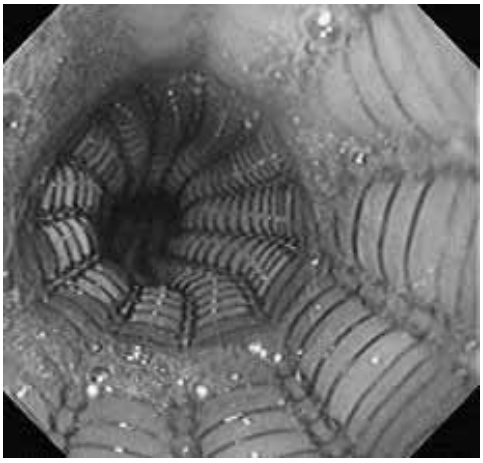
A pre-mounted Ultraflex stent or Wallstent (either a Wallstent II or a Flamingo Wallstent) is then advanced over the wire. The Wallstent is deployed by retracting the constraining outer sheath, whereas the Ultraflex stent is deployed by pulling a ring attached to the suture ring.
As a first step prior to insertion, the Z-stent needs to be back-loaded into its delivery catheter. Then, the Z-stent is deployed by removing a peel-away sheath and pulling a compression catheter back over a pushing catheter.

Both the Ultraflex stent and the Wallstent shorten during expansion, which must be taken into consideration when positioning the introduction system. In order to prevent migration of the stent upon release from the introduction system, the system should not be advanced too far distally. An advantage of the Wallstent is

that it can be recaptured (if not expanded over more than 50%) by advancing the constraining sheath and repositioning the entire stent. The stent should be 2-4 cm longer than the stricture to allow for a 1-2 cm extension above and below the proximal and distal tumor margins. For stents placed across the gastro-esophageal junction, stent length is guided by the rule that the proximal covered portion of the stent should lie at least 1-2 cm above the tumor margin, whereas the distal covered portion should not overlap the tumor margin by more than 1 cm, to prevent ulceration of the posterior wall of the stomach by the distal end of the stent. There is no objection to confirm endoscopically that the upper end of the stent is positioned proximal to the upper tumor margin (Figure 4). However, the endoscope should not be passed through the stent to avoid stent dislodgment from friction with the endoscope.

Thanks to their mechanical properties, both the Ultraflex stent and the Wallstent, whether fully expanded, partially expanded, unexpanded or migrated after release from the introduction system, are easier to reposition or remove endoscopically than the Z-stent. This is done by pulling at the upper rim of the Wallstent or at the lasso attached inside the proximal flange of the Ultraflex stent, causing the radial diameter of the stent to decrease. Stent expansion can best be confirmed by a chest radiograph. Currently, stent placement is an outpatient procedure. Placement of a metal stent takes about 15–20 minutes.

Figure 4: Endoscopic view of the Ultraflex stent immediately after placement.



2.6.5 Complications and recurrent dysphagia

Procedure-related complications after metal stent placement mainly consist of perforation, aspiration pneumonia, fever, bleeding and severe pain, and occur in 5-15% of patients. Delayed complications and recurrent dysphagia following stent placement include hemorrhage, fistula formation, gastroesophageal reflux, stent migration, tumor over- or ingrowth, and food-bolus obstruction, and occur in 30-45% of patients. Minor complications are mild retrosternal pain and gastro-esophageal reflux, which are reported by 10-20% of patients.

Perforation

Perforation occasionally occurs after stent placement; sometimes following dilation of an obstructing tumor to facilitate placement of the stent. Perforation is treated with conservative treatment including naso-duodenal tube feeding, nil per mouth and antibiotics. Placement of a second stent to seal the perforation is sometimes indicated.

Fever

Fever which occurs without evidence of aspiration pneumonia or perforation is most likely to be caused by a mechanical effect of the stent on the tumor, possibly by releasing toxic products from the tumor. Patients usually recover uneventfully after prophylactic treatment with antibiotics.

Hemorrhage

Hemorrhage, including hematemesis and melena, mostly occurs as a late complication of stent placement. It is often unsure whether this is due to the stent placement, progression of the disease, or to a cause unrelated to the tumor and its treatment. During endoscopy the precise source of blood loss is often not discovered. Treatment consists of blood transfusions in case of severe hemorrhage, sometimes in combination with a short course of external beam radiotherapy (e.g. 5 sessions of 4 Gray).

Retrosternal pain

(Transient) retrosternal pain is a frequently reported complication after stent placement, particularly after prior radiation and/or chemotherapy. Golder et al. (73) recorded the daily opioid analgesic requirements of 52 patients from 3 days before until 7 days after stent placement. Twenty-six (50%) patients needed opiates for

chest pain within 48 hours of the procedure compared to 11 (21.2%) patients before stent placement ($p<0.001$). In other studies, figures ranging from 5-50% for chest pain after stent placement have been reported (44, 81, 90, 94). In our experience, mild retrosternal after stent placement can effectively be treated with acetaminophen or one of the non-steroidal anti-inflammatory drugs. Only rarely, opiates are indicated for a period of a few days to maximal 1-2 weeks. Severe pain after stent placement occurs in 1-2% of all patients. In these patients, removal of the stent is sometimes indicated to relief the pain.

Gastro-esophageal reflux

Gastro-esophageal reflux is a common problem among patients with distally located tumors where the distal end of the stent is placed through the lower esophageal sphincter. As a preventive measure, proton-pump inhibitors are prescribed in many institutions to patients with a stent passing the lower esophageal sphincter. Recently, metal stents with an anti-reflux mechanism have been developed to prevent gastro-esophageal reflux. At the distal end of the stent, the cover of the stent is extended beyond the lower metal cage so as to form a "wind sock"-type valve. The first results of this anti-reflux stent were reported in a study including 11 patients. The authors concluded that the anti-reflux stent was effective in preventing gastro-esophageal reflux (74). A study comparing anti-reflux stents (25 patients) with standard open stents (25 patients) showed that 3/25(12%) versus 24/25 (96%) patients, respectively, reported symptoms of gastro-esophageal reflux ($p<0.001$), whereas no differences in dysphagia improvement, complications, or reintervention rate were found (75). These results are promising and will likely reduce the prescription rate of proton-pump inhibitors in these patients.

Stent migration

Stent migration is a common complication with reported incidence rates varying between 5-15% (28, 31, 76, 77). The most frequently used method for re-intervention after stent migration is placement of a second stent. In certain cases, repositioning of a distally migrated stent is possible with the use of a forceps or a snare (78), or placing the endoscope in a retroflexed position (79). We do not recommend using the latter technique, since esophageal perforation may occur. In addition, this method may result in damage to the endoscope (80). If repeated episodes of stent migration occur in the same patient, other palliative treatments such as brachytherapy or laser therapy need to be considered.

From our own experience and from others (77), it is important to realize that stent retrieval after migration is often not indicated, because perforation or obstruction of the digestive tract is uncommon. If a migrated stent causes obstruction of the pylorus or symptoms of pain, or if successful placement of a second stent is impossible, than stent removal should be performed. Several methods of stent retrieval have been described. In case of an Ultraflex stent, this can be done by collapsing the stent with a grasping forceps using the purse string suture attached to the proximal flange of the stent. The most frequently described method however is by decreasing the diameter of the stent with a polypectomy snare at 2-5 cm from the proximal end of the stent (81, 82). Others have used a biopsy forceps in combination with a snare, which requires passage of a double-channel therapeutic endoscope (83). Apart from a snare, one can use endoloops, which may have a greater constriction force than a polypectomy snare (84).

Tumor overgrowth

Tumor overgrowth is the result of progression of the malignancy rather than a failure or a complication of the stent. It affects both ends of the stent at a similar rate and is seen in 10-20% of patients after a mean period of 2-4 months after stent placement (28, 68, 76, 85). Tumor overgrowth can be prevented, at least temporarily, by inserting a stent that is, after expansion, approximately 2-4 cm longer than the malignant stricture to allow for a 1-2 cm extension above the proximal and below the distal end of the tumor.

The most frequently used method for the treatment of tumor overgrowth is placement of a second stent. In addition, laser therapy or argon plasma coagulation can be used to debulk the tumor. In case of placement of a second stent, the stent is placed proximal or distal to the previously placed stent with a part of the second stent overlapping the primary stent.

In our experience, recurrent dysphagia due to nonmalignant obstructive tissue, such as granulation tissue, reactive hyperplasia and fibrosis at the proximal or distal end of the stent is an unlikely event. Mayoral et al. (86) however reported this cause of recurrent dysphagia in more than 30% of their patients at a mean interval of 22 weeks after stent placement. We observed the development of this nonmalignant tissue in a number of patients undergoing endoscopy for reasons other than recurrent dysphagia. It was predominantly found at the proximal end of the stent but did not appear to cause dysphagia.

Other causes of recurrent dysphagia

Food bolus obstruction occurs fairly common with reported rates of 5-15% (28, 68, 76, 85). It can successfully be treated by endoscopic stent clearance. However, care should be taken to prevent the stent from migrating while doing this. Prevention of food bolus obstruction can be achieved by providing eating instruction, including chewing the food thoroughly and drinking sparkling drinks during and after a meal.

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3

Diagnostic procedures and treatment strategies for esophageal cancer in the Netherlands

Translated from:
Diagnostiek en behandeling van het slokdarmcarcinoom in Nederland: veel variatie in de tweede lijn.

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ABSTRACT

Objective: To survey the diagnostic procedures and treatment strategies currently employed in hospitals in the Netherlands for patients with esophageal carcinoma.

Methods: A questionnaire was sent to all clinicians working in the field of gastroenterology in the Netherlands. This questionnaire focused on clinical preferences regarding diagnostic procedures and treatment strategies for esophageal cancer. Also, hypothetical patient vignettes were presented to investigate which factors affected choice of treatment, in particular surgical treatment.

Results: The response rate was 64%. Almost 90% of the clinicians treated fewer than 20 patients annually, mostly in their own hospital. Computer tomography was the most frequently used staging procedure; endoscopic ultrasound was less frequently used (42% used it in less than half of patients). The treatment choice for the patients vignettes varied widely among clinicians. Factors influencing the choice to operate or not were metastases, loco-regional tumor ingrowth, poor general health, and advanced age, with 8%, 22%, 20%, and 53% respectively of the clinicians still considering surgery in the presence of one of these factors as opposed to 99% if none of these factors were present. Surgeons opted more often for operation than internists and gastroenterologists. Stent placement was the most frequently chosen method to palliate malignant dysphagia.

Conclusions: There is a wide variation in the use of diagnostic procedures and treatment strategies for patients with esophageal cancer in the Netherlands. This stresses the need for scientifically based practice guidelines, taking into account specific patient and tumor characteristics.

INTRODUCTION

Esophageal cancer is a disease with a high mortality, as reflected by a 5-year survival rate of 10% (1). Annually, almost 400,000 new patients are diagnosed worldwide, of which 1100 patients are diagnosed in the Netherlands. This makes esophageal cancer the eighth most common cancer, and sixth on the list of cancer mortality causes (2). In the industrialized world, in spite of a stable or even falling incidence of squamous cell carcinoma of the esophagus, the total incidence of esophageal carcinoma has risen in recent years as the result of a marked rise in the incidence of adenocarcinoma (3-5).

Optimal staging of the disease is important to determine the most suitable treatment strategy, either curative or palliative. In addition, this information may predict the prognosis for individual patients. Furthermore, uniform treatment strategies are important in optimizing patient care. As general guidelines for the diagnosis and treatment of esophageal cancer have not been established in many countries, including the Netherlands, we investigated whether this affects the currently used diagnostic procedures and treatment strategies amongst Dutch clinicians working in the field of gastroenterology. This included also the frequency of diagnostic procedures with which these are applied and the criteria in choosing between specific curative and palliative treatment strategies.

METHODS

In April 2001, a written questionnaire was sent to all Dutch clinicians (internists, gastroenterologists and surgeons) working in the field of gastroenterology, listed as MD-members of the Netherlands Society of Gastroenterology (n=667). After 4 weeks a reminder was sent.

A total of 426 (64%) questionnaires were returned. Twenty-seven questionnaires were returned unanswered because the clinician had retired or was no longer working in a hospital. Sixty-three clinicians were not involved in the care for patients with esophageal cancer. These questionnaires were excluded, leaving 336 questionnaires for analysis.

The questionnaire included 7 questions, all multiple choice (see Appendix). The first four questions involved general characteristics of the clinicians, including their specialization, the type of hospital (university or general hospital) where they

worked, the number of new patients with esophageal cancer they saw annually, and whether such patients were generally treated in the clinicians' own hospital or were referred to another (university) hospital. Question 5 investigated the type of diagnostic procedures and the frequency with which these were applied. Question 6 investigated which treatment the clinician would have chosen for specific categories of patients with esophageal cancer presenting with dysphagia. These categories were presented as patient vignettes (Table 1), and the therapeutic options comprised commonly applied curative and palliative treatments. Patient vignettes were chosen with varying variables, such as age (55 or 80 years), general health (good or poor), and tumor characteristics (presence of loco-regional tumor ingrowth or metastases). The final question examined the forms of palliative treatment used in treating malignant dysphagia.

We analyzed the influence of specialization, the type of hospital the clinician was working and the number of patients treated annually by each clinician, on the use of various staging procedures and palliative treatments with the Kruskal Wallis test, and, if appropriate, with logistic regression (Question 5 and 7). The X^2 test was used for analyzing the influence of specialization, type of hospital, and number of patients treated annually, on the preferred treatment option for each patient vignette (Question 6). The number of clinicians who chose for surgery on the basis of the various patient vignettes was compared with the McNemar's test.

Table 1: Description of the variables in patient vignettes described in question 6; all patients were described as having esophageal cancer causing dysphagia.

Question	Age	General condition	Loco-regional tumor ingrowth (T_4)	Metastases
6A	55	Good	No	No
6B	55	Good	No	Yes
6C	55	Good	Yes	No
6D	55	Poor	No	No
6E	80	Good	No	No
6F	80	Good	Yes	No

Table 2: General characteristics of the clinicians with completed questionnaires (n=336).

	N (%)
Clinicians registration	
Internal medicine	111 (33)
Gastroenterology	117 (35)
Surgery	108 (32)
Hospital	
University Hospital	75 (22)
General Hospital	259 (77)
Both	2 (1)
Number of new patients with esophageal cancer treated by clinician annually	
<5 patients	94 (28)
5-20 patients	197 (59)
20-50 patients	32 (10)
>50 patients	13 (4)
Hospital where staging and treatment of patients is performed	
Never referred to other (university) hospital	153 (46)
Sometimes (<50%) referred to other (university) hospital	104 (31)
Mostly (>50%) referred to other (university) hospital	44 (13)
Always referred to other (university) hospital	33 (10)

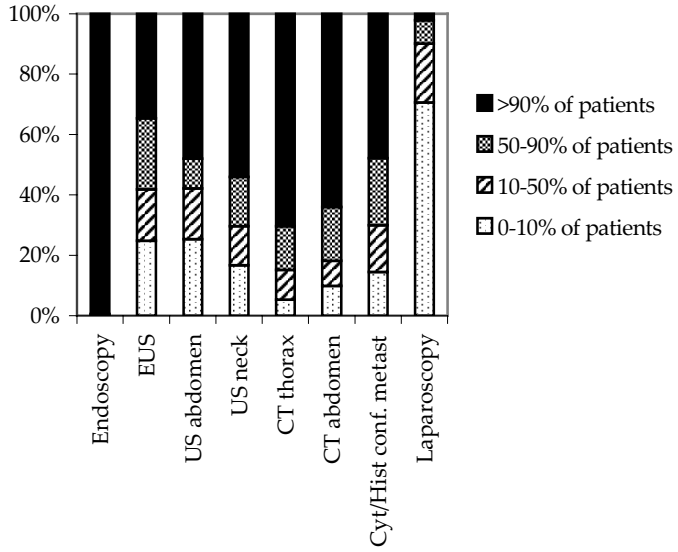
RESULTS

The number of analyzable questionnaires from the three groups of specialists (internal medicine, gastroenterology and surgery) was similar (Table 2). Eighty-seven percent of the clinicians treated 20 patients or less with esophageal cancer annually. Overall 77% of the total number of clinicians, and 73% of the clinicians treating less than 20 patients annually, preferred treating patients with esophageal cancer in their own hospital.

Diagnostic procedures

The frequency distribution of the various diagnostic and staging procedures employed by the clinicians is shown in Figure 1. Computer tomography (CT) was the most frequently used procedure for tumor staging, while endoscopic ultrasound (EUS) was far less often employed. Clinicians in university hospitals employed more often EUS for staging than those working in general hospitals ($p<0.001$). On the other hand, abdominal ultrasound was more frequently used in general hospitals ($p=0.001$). All three specialist groups used the various diagnostic and staging procedures with equal frequency.

Figure 1: The use of different diagnostic and staging procedures for patients with esophageal cancer by clinicians in the Netherlands (Question 5, n=336).



Preferred treatment for patient vignettes with specific characteristics

There was considerable divergence in the treatments chosen on the basis of various patient vignettes (Table 3). The first case of a 55-years-old patient in a good general condition without evidence of metastatic disease (Question 6A) was the only case in which there was a large concordance for the preferred therapy, being surgical esophagectomy. For the other patients a considerable variation existed in preferred treatment choice. For instance, for a 55-year-old patient in a good general condition with loco-regional tumor ingrowth (Question 6C), 39% preferred a combination of external beam and intraluminal radiation, but surgery (22%), chemotherapy (19%), stent placement (27%), and external beam radiation alone (15%) were also frequently chosen.

Surgeons more often preferred surgery, despite evidence of loco-regional tumor ingrowth ($p<0.001$), a poor general condition ($p<0.001$), or a higher age of the patient ($p<0.001$) than internists and gastroenterologists (Figure 2). The treatment choices of clinicians working in university hospitals did not differ from those working in general hospitals. However, clinicians treating less than 20 patients annually more often chose stent placement for elderly patients in a good general condition without

evidence of metastatic disease than did clinicians treating more than 20 patients annually (22% versus 7%, p=0.009), who more often opted for surgery for this type of patient (70% versus 50%, p=0.03). For the other patient vignettes no major differences were found between clinicians treating more or less than 20 patients annually.

It was clear that metastatic disease had a major influence on the decision whether to operate or not, with only 8% preferring surgery for a 55-year-old patient in a good general condition with metastases compared to 99% for the 55-year-old patient without metastases (p<0.001) (Table 3). Other factors that made the decision to operate less likely in patients without metastatic disease were loco-regional tumor ingrowth with a reduction to 22% (p<0.001), a poor general condition with a reduction to 20% (p<0.001), and advanced age with a reduction to 53% (p<0.001). For a patient with loco-regional tumor ingrowth without metastases, the 22% preference for surgery for a 55-year-old patient was reduced to 6% for an 80-year-old patient (p<0.001). From these results it can be concluded that metastatic disease influenced the choice against surgery far more than loco-regional tumor ingrowth or a poor general condition, and that the factor advanced age alone influenced the choice least, with 8%, 22%, 20%, and 53%, respectively, still preferring surgery (p<0.001).

Palliative treatments

Stent placement was the preferred palliative treatment for malignant dysphagia (Figure 3). Sixty percent of the clinicians opted for stent placement in the majority of their patients with inoperable esophageal cancer and dysphagia. External beam radiation, intraluminal radiation or their combination were less frequently used for palliation, only 22% using any form of radiotherapy in the majority of their patients. Dilation as sole palliative treatment was infrequently used, 77% of the clinicians never or only rarely (0-10%) used this technique for palliation.

Table 3: Treatment options chosen by clinicians (n=336) in the Netherlands for specific patients vignettes with esophageal carcinoma, in percentages*.

Patient vignette	Surgery	Chemo-therapy	Stent	ERT	ILT	ERT+ ILT	Dilata-tion
6a: 55 yr, good general cond, no metastases	99	6	0	0.3	0	0.3	0
6b: 55 yr, good general cond, cervical lymph node metastases	8	24	41	13	16	37	2
6c: 55 yr, good general cond, tumor growth into pleura (T4)	22	19	27	15	8	39	1
6d: 55 yr, poor general cond, no metastases	20	5	40	8	14	31	2
6e: 80 yr, good general cond, no metastases	53	1	20	4	7	26	0.3
6f: 80 yr, good general cond, tumor growth into pleura (T4)	6	4	58	10	12	27	2

ERT = external beam radiation, ILT = intraluminal radiation
* Because clinicians could select more than one treatment option, total amount can exceed 100%

Figure 2: The frequency of considering surgery for specific patient groups with esophageal cancer by surgeons (n=108), internists (n=111), and gastroenterologists (n=117). * p<0.001

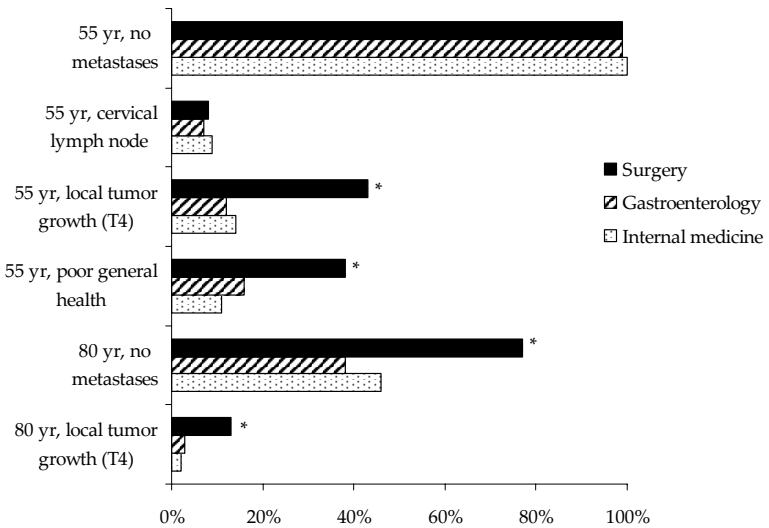
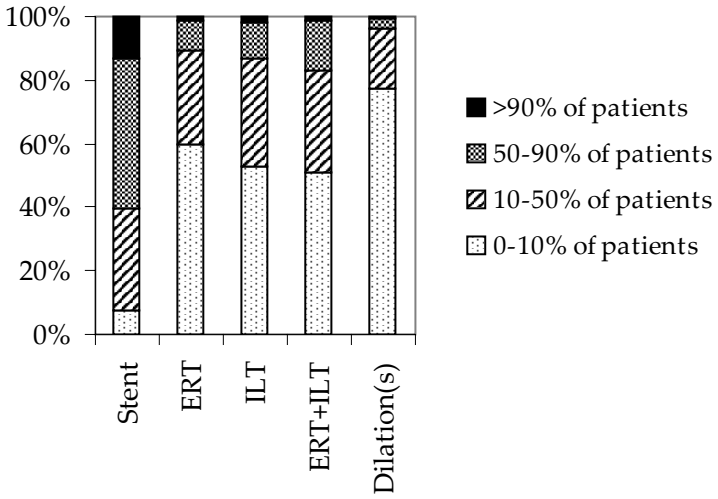


Figure 3: The use of various palliative treatments for patients with malignant dysphagia (ERT = external beam radiation, ILT = intraluminal radiation) (Question 7, n=336).



DISCUSSION

Clinicians in the Netherlands were found to use a wide variety of strategies in staging and treating patients with esophageal cancer. Since 87% of the clinicians see less than 20 patients with esophageal carcinoma annually and the majority treats these patients in their own hospital, it is our opinion that consensus on the use of diagnostic procedures and treatment modalities for patients with esophageal cancer is highly desirable.

Not surprisingly, endoscopy was performed by all clinicians for diagnosing the tumor and sampling of biopsies. Nowadays, endoscopic ultrasound (EUS) is considered the most accurate pre-operative procedure for tumor T-staging (local tumor extension) and N-staging (regional lymph node involvement) (6-10). However, only 35% of the clinicians used EUS regularly despite the fact that this technique is available in all regions in the Netherlands (Figure 1). EUS was employed far less frequently in general hospitals than in university hospitals. This can be explained by the fact that experience is essential to perform EUS and, consequently, its use in the Netherlands is mainly limited to hospitals with a critical number of patients with esophageal carcinoma, which are, in general, the university hospitals and some f the larger general hospitals.

Computer tomography (CT) and abdominal ultrasound are both widely used in determining the possible presence of metastases (M-stage) from esophageal cancer (11-14). This could also be concluded from the answers of our questionnaire. However, new versions of the CT have a higher sensitivity and specificity to determine metastases and, for the future, CT will therefore probably be preferable to abdominal ultrasound (15, 16).

It was reassuring to find that surgery was unanimously selected as treatment of choice in the young (55-year-old), uncomplicated patient. The divergence of opinion in the more complicated cases reflects our current state of ignorance as to the optimal treatment for patients with extensive and/or metastatic disease. A practice guideline for diagnosing, staging and treating esophageal cancer was published by the American College of Gastroenterology in 1999 (17). This report gave an overview of the diagnostic and treatment modalities for esophageal carcinoma and concluded that due to the many uncertainties and the generally unsatisfactory state of the current management options, patients should be encouraged to enter clinical trials in order to improve the staging and treatment strategies. Guidelines were also published in France recommending clear decision-tree models for determining therapeutic strategies (18). The authors concluded that there was no standard treatment for the majority of patients and several options were presented. In these guidelines, treatment options depended on tumor stage. However, from our survey it can be concluded that patient characteristics, such as age and general condition, should also be taken into consideration in determining therapeutic strategy. Although guidelines based on the literature can go some way in standardizing the management of individual patients, there remains an urgent need for randomized trials for various tumor stages and age groups, comparing surgery to non-surgical and palliative treatments, both from the point of view of survival and of quality of life.

For patients judged to be inoperable, several treatment modalities are available. The results of palliative chemotherapy are improving, particularly through the use of new agents and new combinations (19). However, chemotherapy at present does not appear to be popular with Dutch clinicians (the use of chemotherapy varied between 1-24% for the different patient vignettes). External beam radiation alone or in combination with intraluminal radiation is a rather demanding treatment, usually involving 25 treatment sessions of external beam radiation in combination with 2 treatment sessions of intraluminal radiation. This treatment is usually reserved for patients in a good clinical condition, however being inoperable because of local-regional tumor ingrowth. A median survival of 8-13 months has been reported for

this treatment modality (20-22). For the majority of patients with inoperable esophageal carcinoma stent placement or intraluminal radiation are considered the most practical and effective options to improve dysphagia (23-27). Our survey indicates that of these two palliative modalities, stent placement is the most frequently used method in the Netherlands.

In conclusion, this survey indicates that at present there are wide variations in the strategies for diagnosis, staging and treatment of patients with esophageal cancer in the Netherlands. There is a need for more evidence-based approaches to both the use of diagnostic procedures and the choice of treatment. Based on the recently published guideline 'Esophageal carcinoma' of the Comprehensive Cancer Center and the guideline of the Dutch Institute for Healthcare (CBO) which is currently being developed (publication expected in the fall of 2004), a more uniform and successful management of esophageal cancer in the Netherlands will be achieved. It would be interesting to repeat this survey within 1-2 years after publication of these guidelines, which would clarify if guidelines are the optimal instrument to achieve this goal.

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APPENDIX

Questionnaire

1. What is your clinician registration?
   - O Internal medicine
   - O Gastroenterology
   - O Surgery

2. Are you working in a university hospital or general hospital?
   - O University hospital
   - O General Hospital

3. How many new patients with esophageal carcinoma do you treat annually?
   - O 0 (end of questionnaire)
   - O < 5
   - O 5-20
   - O 20-50
   - O > 50

4. Is staging and treatment of esophageal carcinoma being performed in your own hospital or are such patients referred to another (university) hospital?
   - O Patients are never be referred
   - O Patients are sometimes (<50%) referred
   - O Patients are often (>50%) referred
   - O Patients are always referred

5. How often do you use the following diagnostic and staging procedures to establish further treatment?

a)	Endoscopy	0-10% / 10-49% / 50-90% / >90%
b)	Endoscopic ultrasound	0-10% / 10-49% / 50-90% / >90%
c)	Abdominal ultrasound	0-10% / 10-49% / 50-90% / >90%
d)	Ultrasound of the neck	0-10% / 10-49% / 50-90% / >90%
e)	CT thorax	0-10% / 10-49% / 50-90% / >90%
f)	CT abdomen	0-10% / 10-49% / 50-90% / >90%
g)	Cytological/histological confirmation of metastases (if appropriate)	0-10% / 10-49% / 50-90% / >90%
h)	Laparoscopy	0-10% / 10-49% / 50-90% / >90%
i)	Other …..……	0-10% / 10-49% / 50-90% / >90%

6. Which therapy do you prefer for the following type of patients with esophageal cancer causing dysphagia?
   a) a 55-year old patient in a good general condition and without metastases.
      - O surgery
      - O chemotherapy
      - O metal stent placement
      - O external beam radiation
      - O intraluminal radiation (brachytherapy)
      - O external beam +intraluminal radiation
      - O (several) dilation (sessions)
      - O other ……..

   b) a 55-year old patient in a good general condition and with metastases in the cervical lymph nodes.
      See answering categories as in question 6A

   c) a 55-year old patient in a good general condition and with tumor growth into the pleura (stage T_4), without metastases.
      See answering categories as in question 6A

   d) a 55-year old patient in a poor general condition due to severe COPD, without metastases.
      See answering categories as in question 6A

   e) an 80-year old patient in a good general condition and without metastases.
      See answering categories as in question 6A

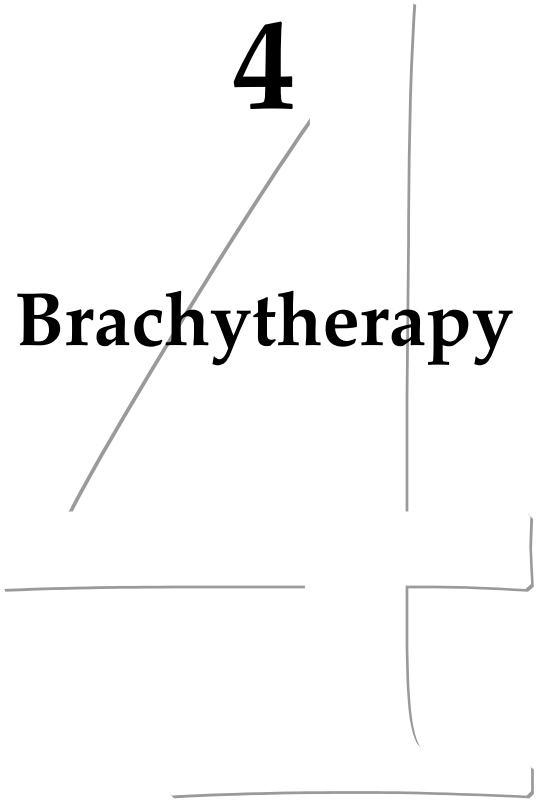
   f) an 80-year old patient in a good general condition and with tumor growth into the pleura (stage T_4), without metastases.
      See answering categories as in question 6A

7. How often do you use the following palliative treatments for malignant dysphagia?

a) metal stent placement	0-10% / 10-49% / 50-90% / >90%
b) external beam radiation	0-10% / 10-49% / 50-90% / >90%
c) intraluminal radiation (brachytherapy)	0-10% / 10-49% / 50-90% / >90%
d) external beam+intraluminal radiation	0-10% / 10-49% / 50-90% / >90%
e) (several) dilation (sessions)	0-10% / 10-49% / 50-90% / >90%
f) other ……	0-10% / 10-49% / 50-90% / >90%

4

Brachytherapy



4A

High Dose Rate Brachytherapy for the palliation of malignant dysphagia

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ABSTRACT

Background and purpose: High dose rate (HDR) brachytherapy is a commonly used palliative treatment for esophageal carcinoma. We evaluated the outcome of HDR brachytherapy in patients with malignant dysphagia.

Material and methods: A retrospective analysis over a 10-year period was performed of 149 patients treated with HDR brachytherapy, administered in one or two sessions, at a median dose of 15 Gy. Patients were evaluated for functional outcome, complications, recurrent dysphagia, and survival.

Results: At 6 weeks after HDR brachytherapy, dysphagia scores had improved from a median of 3 to 2 ($n=104$; $p<0.001$), however dysphagia had not improved in 51 (49%) patients. Procedure-related complications occurred in 7 (5%) patients. Late complications, including fistula formation or bleeding, occurred in 11 (7%) patients. Twelve (8%) patients experienced minor retrosternal pain. Median survival of the patients was 160 days with a 1-year survival rate of 15%. Procedure-related mortality was 2%. At follow-up, 55 (37%) patients experienced recurrent dysphagia. In 34 (23%) patients a metal stent was placed to relief persistent or recurrent dysphagia.

Conclusion: HDR brachytherapy is a moderately effective treatment for the palliation of malignant dysphagia. The incidence of early major complications is low, however, persistent and recurrent dysphagia occur frequently, and require often additional treatment.

INTRODUCTION

Over 50% of patients with a carcinoma of the esophagus or gastric cardia have inoperable disease at presentation due to advanced local tumor progression, metastases or a poor general condition. Most patients require palliative treatment for dysphagia.

Treatment options presently available for palliation include self-expanding metal stent placement, laser therapy, external beam radiation sometimes in combination with high dose rate (HDR) brachytherapy, and HDR brachytherapy as a single treatment (1). The disadvantage of laser therapy is that repeated treatment sessions are required to achieve and maintain adequate palliation. Self-expanding metal stent placement has achieved wide popularity, but metal stents are expensive (2-6). For patients with extensive local-regional tumor growth and a good clinical condition, a combined treatment of HDR brachytherapy with external beam radiotherapy might result in good local tumor regression and relief of dysphagia (7-12). The treatment schedule mostly involves a total of 50 Gy external beam radiation delivered in 25 fractions combined with one or two session of HDR brachytherapy (10-15 Gy), and is often too intensive for inoperable patients with metastases or a poor general condition. A single treatment with HDR brachytherapy could be an attractive alternative for the palliation of malignant dysphagia in these patients.

To date, ten studies have been published reporting that in the majority of patients dysphagia can be palliated by a single session of HDR brachytherapy with doses varying between 7.5 and 20 Gy, including two studies of which the results have only been presented in abstract form (13-22). The majority of these studies were small and results varied widely. Therefore, we performed a retrospective analysis of patients treated by HDR brachytherapy over a 10-year period. Patient records were evaluated for functional outcome, complications, recurrent dysphagia, and survival.

MATERIALS AND METHODS

From 1-1-1990 to 31-12-1999, 310 patients with an inoperable carcinoma of the esophagus were treated by HDR brachytherapy. Patients were excluded from analysis if they had received HDR brachytherapy in combination with external beam radiotherapy (n=148), or if they had tumor recurrence after a surgical esophageal resection (n=13). The remaining 149 patients, treated by HDR brachytherapy only, were selected for analysis. These patients had been judged to be inoperable and ineligible for external beam radiation with curative intent because of a poor medical condition (47%), or metastases (53%).

Prior to HDR brachytherapy, the proximal and distal ends of the tumor were identified endoscopically and a guide wire was left, over which the flexible applicator was passed down the esophagus. Dilation up to 10 mm was necessary in 20 (13%) patients. In 31 (21%) patients a feeding tube (Charrière 14) was used as applicator for HDR brachytherapy. A median dose of 15 (range 6-20) Gy was administered with the radioactive source ^{192}Iridium at 1 cm from the source axis of the applicator in one (87%) or two (13%) sessions. The dose distributed to the surface of the tumor (5 mm from the source axis) amounted 200% of the prescribed dose. The dose administrated at 12.5 mm from the source axis was 65% (at 7.5 mm from the surface of the tumor). The mean application time of the procedure was 995 ± 416 seconds (16 min 35 sec, range 190 - 2378 sec). The standard active length of application was the tumor length plus two centimeters extra at both ends of the tumor. The mean active length was 13.6 ± 2.8 cm (range 7.0 –23.0 cm). Sucralfate was prescribed for a period of 4 weeks after HDR brachytherapy as a prophylactic measure for odynophagia (23).

For evaluation, dysphagia was scored according to Ogilvie et al. (24) as: grade 0: ability to eat a normal diet; grade 1: ability to eat some solid food; grade 2: ability to eat some semisolids only; grade 3: ability to swallow liquids only; grade 4: complete dysphagia. Accurate dysphagia scoring on the day of the first session of HDR brachytherapy and at 6 weeks after therapy was possible in 104 patients. Complications, recurrent dysphagia and survival were analyzed for the total group of 149 patients. The results are expressed as means ± SD; dysphagia score and survival are expressed as medians. Dysphagia scores before treatment and 6 weeks after treatment were compared with Wilcoxon signed-ranks test. Survival was analyzed with the Kaplan-Meier method.

RESULTS

Clinical characteristics

The mean age of patients was 74 (range 43-93) years, 44% were female (Table 1). The mean tumor length was 6.8 (range 1-17) cm. Some more squamous cell carcinoma (56%) than adenocarcinoma (42%) were identified.

Table 1: Clinical characteristics of 149 patients with an inoperable esophagogastric carcinoma treated with HDR brachytherapy.

Age (y)	74 ± 11
Gender (M / F)	83 / 66
Mean Tumor Length (cm)	6.8 ± 3.3
Tumor Histology	
Squamous cell carcinoma	83 (56%)
Adenocarcinoma	63 (42%)
Other	3 (2%)
Location of Tumor (distance from incisors)	
Proximal (< 25cm)	18 (12%)
Middle (25-35 cm)	79 (53%)
Distal (> 35 cm)	41 (28%)
Cardia	11 (7%)
Total dose of radiation (Gy)	
6 ≤ 7.5	5 (3%)
10 ≤ 12	22 (14%)
15	115 (77%)
16 ≤ 20	8 (6%)

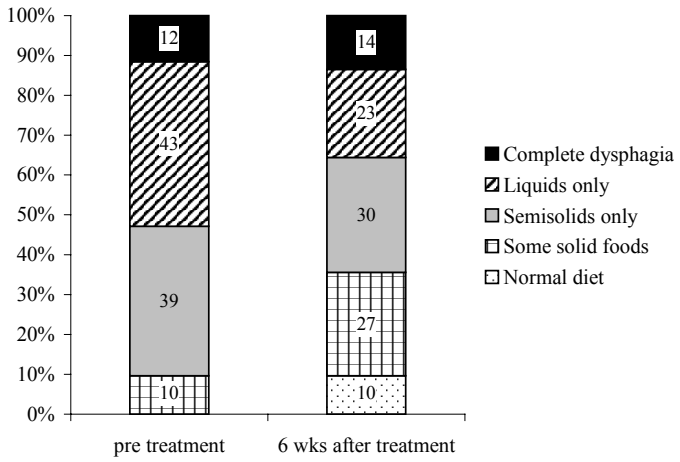
Outcome and survival

At 6 weeks after HDR brachytherapy, the dysphagia score had improved from a median of 3 to 2 (n=104; p<0.001). Dysphagia improved in 53 (51%) of the 104 patients; 67 (64%) of these patients were able to eat solids or semi-solids (Figure 1). The median survival of the patients was 160 days with a 3, 6, and 12 months survival rate of 72%, 43% and 15%, respectively. The procedure-related mortality was 2% (see below). The majority of the remaining patients (81%) died from tumor progression, 7% from unrelated causes, and in 10% of the patients the cause of death was unknown. One person was still alive at 27 months after HDR brachytherapy.

Complications and recurrent dysphagia

Major complications occurred in 18 (12%) patients, 7 (5%) of these occurred in the first week after HDR brachytherapy (Table 2). Two early complications were fatal. One patient suffered from severe esophageal edema necessitating a feeding tube, and died 19 days later from respiratory failure caused by aspiration pneumonia. Another patient developed stridor and dyspnea at the day after treatment. At the request of the patient and his family, no further procedures were performed. This patient died 24 hours after admission from respiratory failure.

Figure 1: Dysphagia scores of patients with esophagogastric carcinoma before and 6 weeks after treatment with HDR brachytherapy (n=104).



One patient developed hematemesis 3 days after HDR brachytherapy, which resolved spontaneously. Another patient developed an esophagorespiratory fistula following dilation for persisting complete dysphagia, three days after HDR brachytherapy. The fistula was closed by placement of two coated metal stents. One week later, this patient died from cardiac failure. Three patients reported severe chest pain after HDR brachytherapy, but the pain gradually diminished after some weeks.

Six patients suffered late hematemesis and/or melena after a median of 8 months (range 2-17 months), all in the presence of recurrent tumor growth. Three of these patients died from massive hematemesis. Of the three survivors one received another session of HDR brachytherapy, which stopped the bleeding. Another patient had recurrent non-fatal episodes of hematemesis at 4 and 8 months after a second treatment of HDR brachytherapy. The third patient only needed a blood transfusion. Five patients developed an esophagorespiratory fistula after a median of 11 months (range 6-15 months). Of these, one developed a fistula at two weeks after a second episode of HDR brachytherapy (11 months after the initial treatment) and died one week later from this complication. One patient who underwent four dilation sessions over a period of 4 months for tumor recurrence, had a fistula diagnosed one week after the last dilation. Another patient developed a fistula after a palliative resection for persistent tumor, followed by external beam radiation and

Table 2: Complications and recurrent dysphagia in 149 patients with an inoperable esophagogastric carcinoma treated with HDR brachytherapy

	N (%)
Major Complications	18 (12%)
≤ 7 days	
Bleeding	1
Fistula	1
Aspiration pneunomia	1
Stridor	1
Severe pain	3
> 7 days	
Bleeding	6
Fistula	5
Minor Complications	12 (8%)
Mild pain	12
Recurrent Dysphagia	55 (37%)
Tumor recurrence	40
Late radiation effects	6
Food bolus obstruction	4
Strictures (unknown cause)	5

dilation. The two remaining fistulas developed in the presence of recurrent tumor growth in the esophagus 1 year and 15 months, respectively, after HDR brachytherapy.

Minor complications (Table 2) consisted of temporary mild chest pain, which was reported by twelve (8%) patients following HDR brachytherapy. Almost all these patients required, at least temporary, analgesics.

HDR brachytherapy failed to improve the dysphagia score in 51 (49%) of the 104 patients with documented 6 week dysphagia scores (Figure 1). Twenty-one (41%) of these patients were then treated with the placement of a conventional endoprosthesis or a self-expanding metal stent (n=12), a feeding tube (n=3), a PEG (n=3), dilation (n=2), or a palliative resection (n=1). Twenty (39%) patients were not treated and remained on a semi-solid or liquid diet. In another 4 patients, the dysphagia score improved after the evaluation at 6 weeks, while in 6 patients persistent dysphagia was due to a variety of reasons, in three of whom endoscopic examination showed no evidence of a stricture.

Fifty-five of 149 (37%) patients developed recurrent dysphagia (Table 2), after a median of 3 months (range 1-26 months), due to tumor recurrence (n=40), late radiation effects such as fibrosis, necrosis or ulceration (n=6), food bolus obstruction (n=4), or a stricture in the esophagus due to an unknown cause (n=5). Recurrent dysphagia was treated by stent placement (n=22), dilation (n=12), a second course of HDR brachytherapy (n=6), placement of a feeding tube or a PEG (n=3), or no further treatment (n=12).

DISCUSSION

HDR brachytherapy is a commonly used treatment modality for palliation of malignant dysphagia. The group of patients in this study was considered to be ineligible for a combination treatment of external beam radiation and HDR brachytherapy, due to poor general condition or metastases. Patients were predominantly treated with a single session of HDR brachytherapy of 15 Gy. In the majority of patients the procedure could be performed as a day-case procedure, which minimized hospitalization in this group of patients with a short live expectancy.

Because of the retrospective nature of the study, it is possible that the incidence of complications and recurrent dysphagia were underestimated. However, most patients remained under out-patient surveillance during the remainder of their life. Accurate dysphagia scoring on both the day of the first HDR brachytherapy session and at 6 weeks after therapy was possible in 104 patients. Thirteen of the other 45 patients died before the 6 weeks follow-up after brachytherapy, and for the remaining 32 patients the 6 weeks dysphagia scores were missing or not well documented. However, the dysphagia scores at the time of HDR brachytherapy (day 0) of these 45 patients, were not significantly different from those of the group with accurate 6 weeks data (data not shown).

The dysphagia score improved in only 51% of these patients. This is a disappointing result, because dysphagia is usually the indication for palliation. In a retrospective study by Giles Rowland and Pagliero (15), reporting the results of palliation with HDR brachytherapy in 40 patients (Table 3), improvement of dysphagia occurred in 65% of the patients. In a retrospective study performed by Brewster et al. (13), improvement of the dysphagia score occurred in 54% of 197 patients, which is comparable to our results. In a prospective study by Jager et al. (17), the dysphagia score improved in 67% of 88 patients, but these authors included 7 (8%) patients with early stage disease, and these patients were treated with a combination of internal and external beam radiation.

Table 3: Overview of studies using HDR brachytherapy for palliation of patients with an inoperable esophagogastric carcinoma.

Author	N	Dose	Dysphagia Improved	Complications	Recurrent dysphagia	Survival
Giles Rowland et al. 1985 (15)	40	15Gy/1x	65%	12.5% esophagitis	?	?
Low et al. 1992 (20)	12	15Gy/1x	83%	33% esophagitis, 17% pain, 17% pyrexia, 8% bleeding	30%	?
Harvey et al. 1993 (16)	22	10: 20Gy/3x 12: 12.5Gy/1x	90% 92%	30% 80% esophagitis	30% 39%	4 months 5.8 months (mean)
Brewster et al. 1995 (13)	197	7.5-20Gy/1x	54%	2% severe complications	?	136 days (median)
Jager et al. 1995 (17)	88	15Gy/1x	67%	34% retrosternal pain, 1% hematemesis, 6% fistulae	37%	5.5 months (median)
Kulhavy et al. 1995 (18)	A:12 B:14 C:14 D:11	A: 10Gy/1x B: 12Gy/1x C: 15Gy/1x D: 18Gy/1x	3/4 8/8 6/6 3/7	0% 0% 0% 9% fistulae	17% 14% 7% 27%	?
Leung et al. 1995 (19)	10	7.1-60Gy/1x	90%	0%	10%	3 months (median)
Sur et al. 1998 (21)	A: 36 B: 68 C: 68	A: 12Gy/2x B: 16Gy/2x C: 18Gy/3x	?	14% strictures, 20% fistulae 25% strictures, 3% fistulae 42% strictures, 11% fistulae	?	10%, 1 year 22%, 1 year 35%, 1year
Present series	149	6-20Gy/1-2x	51%	12% severe complications, 8% mild retrosternal pain	37%	160 days (median)

Were these disappointing results caused by an insufficient radiation dosage? Sur et al. (21) compared different doses of HDR brachytherapy in 172 patients with advanced esophageal cancer. Patients were randomized to receive 12 Gy in 2 sessions, 16 Gy in 2 sessions or 18 Gy in 3 sessions. A preliminary analysis of 68 patients showed that patients who received 12 Gy in 2 sessions did significantly worse than the other two groups in terms of dysphagia-free survival and persistent tumor obstructing the esophageal lumen after treatment. The 12 Gy in 2 sessions arm was therefore discontinued. The authors concluded that the optimal radiation dose ranged between 16 Gy in two sessions and 18 Gy in three sessions. Kulhavy et

al. (18) compared different doses of HDR brachytherapy given in a single fraction. Fifty-one patients received 10, 12, 15 or 18 Gy. From the results of 25 evaluable patients, they concluded that doses of 12-15 Gy were likely to give the best results in terms of relief of dysphagia with minimal morbidity. In our study 137 (92%) patients received 15 Gy in a single fraction. Other doses or fractionation of HDR brachytherapy were chosen for specific reasons such as a greater tumor length, ulceration, or an increased risk of fistula formation. Because of the small number of patients, it was not possible to analyze the influence of dose or fractionation on the outcome of HDR brachytherapy. It is very well possible that a fractionated and/or higher dosage would have improved the results. This question needs further investigation.

Mild esophagitis manifested as pain and increased dysphagia during the first days after treatment is a commonly reported side effect of external beam radiation (12, 23, 25, 26). Data on the occurrence of early esophagitis after HDR brachytherapy vary greatly (Table 3). Jager et al. (17) reported that HDR brachytherapy was well tolerated by their patients with no or very little acute toxicity. Brewster et al. (13) reported that acute symptomatic esophagitis occurred in 3 (2%) patients. In the study by Giles Rowland and Pagliero (15), 5 (12.5%) patients had symptomatic esophagitis for 5-10 days. These results are in contrast with the results from smaller studies by Low et al. (20) and Harvey et al. (16) reporting esophagitis to occur in more than 30% of their patients. Symptoms of esophagitis were not often mentioned by our patients. Radiotherapy can also cause late radiation effects such as ulceration, fibrosis and necrosis, causing strictures in the esophagus (12, 25, 26). This occurred in 6 (4%) of our patients, and was treated by dilation.

The occurrence of early major complications (during or in the first week after HDR brachytherapy) was low in our cohort. Only 7 (5%) major complications were observed, this included three patients with severe pain after HDR brachytherapy which resolved spontaneously. Two early complications were fatal. Other studies have also reported very low major complication rates (Table 3). Recurrent dysphagia after HDR brachytherapy occurred in 37% of our patients, which is similar to the findings of Jager et al. (17). However, Giles Rowland and Pagliero (15) reported only two (5%) patients needing re-treatment after 30 weeks for recurrent dysphagia. In the present study, 34 (23%) patients received a stent for persistent or recurrent dysphagia to improve dysphagia.

Placement of self-expanding metal stents as a first treatment for palliation of dysphagia is nowadays commonly used. An advantage of metal stents could be the rapid improvement of dysphagia in the majority of patients, and the lower

frequency of recurrent dysphagia compared to HDR brachytherapy (2-6). However, major complications seem to occur more frequently after stent placement. A randomized study comparing HDR brachytherapy with the nowadays commonly used placement of a self-expanding metal stent as a first treatment for the palliation of malignant dysphagia is therefore warranted, in order to define the specific indications for both these types of palliation.

HDR brachytherapy in combination with laser therapy could possibly increase the effectiveness. Prior laser therapy should reduce the tumor bulk, thus both speeding up and increasing the improvement of the dysphagia score. In four non-randomized studies, laser plus HDR brachytherapy was studied prospectively and proved to be both safe and effective (27-30). Laser plus HDR brachytherapy was compared with laser therapy alone in two prospective, randomized studies in 39 and 22 patients (31, 32). These studies showed a prolonged dysphagia-free interval after the combination of laser and HDR brachytherapy but there was no difference in survival.

The result of palliative chemotherapy are improving, particularly through the use of new combinations and new agents (33). This can be offered in addition to the treatment to relief dysphagia (HDR brachytherapy or stent placement) for specific patients.

In conclusion, the results of this retrospective study suggest that HDR brachytherapy alone is a safe, but not a very effective treatment for the palliation of malignant dysphagia. The incidence of early major complications is low, however, the occurrence of persistent and recurrent dysphagia leaves much to be desired. Whether results can be improved by higher and/or fractionated radiation doses without jeopardizing safety remains to be studied.

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4B

Predictors of outcome of single dose brachytherapy for the palliation of dysphagia from esophageal cancer

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Submitted

ABSTRACT

Background: Single dose brachytherapy is a commonly used palliative treatment modality for esophageal carcinoma, however a considerable number of patients need additional treatment for persistent or recurrent dysphagia. We aimed to establish predictors for an unfavorable outcome after single dose brachytherapy.

Methods: Between December 1999 and July 2002, 95 patients with dysphagia from inoperable esophageal carcinoma were treated with single dose (12 Gy) brachytherapy. Patients were followed prospectively by monthly home visits by a specialized research nurse. We investigated which patient and tumor characteristics influenced the risk of persistent dysphagia (continuing dysphagia within 4 weeks after treatment necessitating a second treatment) or recurrent dysphagia (occurring more than 4 weeks after treatment) after single dose brachytherapy, using logistic and Cox regression.

Results: In total 42/95 (44%) patients were treated for persistent (n=18) and/or recurrent dysphagia (n=28). Persistent dysphagia (n=18) was caused by persisting obstructing tumor confirmed at endoscopy, and these patients were treated with stent placement. Patients needing dilation before treatment had a higher risk of persistent dysphagia (odds ratio=4.1; 95% CI 1.3-12). There was a trend towards a higher risk of persistent dysphagia for patients previously treated with chemotherapy (odds ratio=3.2; 95% CI 0.81-12). In total, 34 events of recurrent dysphagia occurred in 28 patients, caused by obstructing tumor regrowth (n=26), food bolus obstruction (n=5) or other reasons (n=3). None of the investigated patient and tumor characteristics had a significant association with the risk of developing recurrent dysphagia. In the total group of patients needing additional treatment (42/95), again patients who needed dilation before treatment had a higher risk of persistent and/or recurrent dysphagia (hazard ratio=2.1; 95% CI 1.1-4.1).

Conclusions: Patients with stenotic esophageal tumors that cannot be bypassed or who previously underwent chemotherapy are poor candidates for single dose brachytherapy, and for these patients alternative palliative treatment modalities should be considered.

INTRODUCTION

Over 50% of patients with esophageal cancer have inoperable disease at presentation due to advanced local tumor progression, metastases or a poor general condition (1). The majority of these patients require palliative treatment to relieve progressive dysphagia. At present, several treatment modalities are available for the palliation of dysphagia from esophageal carcinoma. Treatment options most commonly used include metal stent placement (2-6), laser therapy (7, 8), external beam radiation in combination with brachytherapy (9, 10), and brachytherapy as a single treatment (11-14). A disadvantage of laser therapy is that repeat treatment sessions are required to achieve and maintain adequate palliation (7, 8). A combined treatment of external beam radiation with brachytherapy is often too intensive for patients with inoperable, metastatic disease and a poor medical condition. Therefore, in many patients with inoperable disease, placement of a metal stent or single dose brachytherapy are used for the palliation of dysphagia (15).

We performed a randomized trial comparing single dose brachytherapy (n=101) with metal stent placement (n=108) in patients with inoperable esophageal carcinoma (16). This study showed that despite a less rapid improvement of dysphagia, single dose brachytherapy gave a better long term relief of dysphagia. Single dose brachytherapy was also associated with fewer complications compared to stent placement and a benefit in health-related quality of life. A major drawback of single dose brachytherapy was that almost half of the patients needed additional treatment for persistent or recurrent dysphagia after single dose brachytherapy (16).

The consensus guideline of the American brachytherapy society has distinguished several criteria (based on tumor characteristics) to divide patients in good candidates, poor candidates and patients with contraindications for brachytherapy (in combination with external beam radiation) in the definitive and palliative treatment of esophageal cancer (13). Based on these recommendations and the results of our comparative study between single dose brachytherapy and stent placement, we aimed to investigate which baseline patient and tumor characteristics within our study influenced the occurrence of persistent and recurrent dysphagia after single dose brachytherapy. In this way, a more individualized palliative treatment strategy for patients with esophageal cancer may be established.

PATIENTS AND METHODS

Study population

Between December 1999 and July 2002, 209 patients with inoperable esophageal cancer due to metastatic disease and/or a poor medical condition with progressive dysphagia were randomized to single dose brachytherapy (n=101) or metal stent placement (n=108).
Patients were treated with a single dose of 12 Gy brachytherapy (intraluminal radiotherapy) or with a covered Ultraflex stent (Boston Scientific, Natick, MA., USA). Patients were included and treated in three university and six general hospitals in the Netherlands. The study was approved by the Central Committee on Research Involving Human Subjects in The Netherlands.

Inclusion criteria included inoperable cancer of the esophagus or esophagogastric junction due to metastatic disease (as defined by the TNM-classification) and/or a poor medical condition (unfit to undergo surgery) with a dysphagia score of 2-4 on the dysphagia score scale (17), and a written informed consent. Exclusion criteria were a tumor length of more than 12 cm, tumor growth within 3 cm of the upper esophageal sphincter, deep ulceration or a trachea-esophageal fistula, macroscopic or microscopic tumor growth into the tracheal lumen, the presence of a pacemaker, and previous radiation therapy or stent placement.

Of the 101 patients randomized to brachytherapy, 95 patients received the allocated intervention. One patient died before treatment due to progression of the disease, three patients experienced problems during endoscopy prior to brachytherapy including anxiety of the patient (n=1), cardiac arrhythmia (n=1), and inability to pass the tumor (n=1). Two patients did not fulfill the inclusion criteria because of tumor length >12 cm (n=1), and deep ulceration of the tumor (n=1), which had not been reported at the previous endoscopy. In the present analysis, we hence consider 95 patients.

Treatment

Prior to the brachytherapy, an endoscopy was performed. Dilation was performed on indication to a maximum of 11 mm by a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC, USA). The proximal and distal tumor margins were marked by injecting radiographic contrast medium into the submucosa of the esophageal wall through a sclerotherapy needle. Then a guide

wire was left, over which a flexible applicator (Bonvoisin-Gérard Esophageal Applicator, Nucletron, Veenendaal, The Netherlands) with a diameter of 10 mm was passed down the esophagus. A single dose of 12 Gy was administered with the radioactive source ^{192}Iridium at 1 cm from the source axis of the applicator. The standard active length of the application was the tumor length plus two centimeters extra at both ends of the tumor. All patients were consciously sedated with midazolam during the treatment procedure. Sucralfate was prescribed for a period of 4 weeks after brachytherapy as a prophylactic measure for odynophagia. A lifelong daily dose of 40 mg omeprazole was prescribed to patients of whom the active length of application of brachytherapy was below the esophagogastric junction to prevent gastroesophageal reflux after the procedure.

Study endpoints

Persistent dysphagia was defined as continuing dysphagia within 4 weeks after treatment with tumor growth causing obstruction observed at endoscopy necessitating a second treatment. Recurrent dysphagia was defined as recurrent dysphagia occurring at more than 4 weeks after treatment caused by tumor regrowth, food bolus obstruction or other reasons necessitating additional treatment. The choice of the treatment modality for persistent or recurrent dysphagia was made by the responsible physician. Dysphagia was scored as follows: score 0: ability to eat a normal diet; score 1: ability to eat some solid food; score 2: ability to eat some semisolids only; score 3: ability to swallow liquids only; score 4: complete obstruction (17).

Patients were prospectively followed by home visits of one of six specially trained research nurses at 14 days, 1 month and then monthly until one year after treatment. After one year of follow-up, patients were visited every 3 months, and/or telephone calls to the patient and the patients' practitioner were made. If indicated, patients were readmitted for clinical evaluation. All participating clinicians filled out standardized case record forms during control visits, re-treatments and admissions.

Statistics

Improvement in dysphagia score was tested with the Wilcoxon signed-rank test. We investigated which patient and tumor characteristics influenced the occurrence of persistent or recurrent dysphagia. Variables considered in the analyses were age, gender, tumor histology, tumor length (divided into <10 cm and ≥10cm), location of

the tumor (esophagus or esophagogastric junction), presence of metastases, poor general condition (unfit to undergo curative treatment), dysphagia score and WHO performance score before treatment, dilation prior to treatment, and previous chemotherapy treatment. We used logistic regression analysis to estimate univariable and multivariable odds ratios for the risk of persistent dysphagia. For the analysis of recurrent dysphagia and the total group of persistent and/or recurrent dysphagia, we used Cox regression analysis to estimate univariable and multivariable hazard ratios to adjust for time of occurrence of the event and potential survival differences. In all multivariable models, variables were selected in a backward stepwise procedure with $p>0.20$ for exclusion of variables. Univariable Kaplan-Meier curves were constructed to investigate the influence of covariables on the risk of needing additional treatment for persistent and/or recurrent dysphagia. The median survival was calculated using the Kaplan-Meier method. A multivariable Cox regression model was used to evaluate which variable(s) correlated with a shorter survival. We considered a two-sided p-value <0.05 as statistically significant. Calculations were performed with SPSS 10.1 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical outcome

Clinical characteristics of the patient group are given in Table 1. At 30 days after treatment, dysphagia score had improved from a median of 3 to 1 ($p<0.001$). Dysphagia score was improved by at least one grade in 62/84 (74%) of the patients. In total, 12 major complications occurred in 11/95 (12%) patients, of which 3 major complications occurred within 7 days after treatment. Early major complications included perforation (n=1), fever (n=1), and aspiration pneumonia (n=1). Late major complication (>7 days after treatment) included hemorrhage (n=4), fistula formation (n=3), perforation (n=1) and severe pain (n=1). Minor complications occurred in 8/95 (8%) patients, including mild retrosternal pain (n=5), gastro-esophageal reflux (n=1), radiation esophagitis (n=1) and candida esophagitis (n=1).

The median survival was 155 days (95% CI 118-192). Multivariate Cox regression analysis showed that a tumor length of more than 10 cm (hazard ratio 1.6; 95% CI 1.02-2.6, p=0.04), metastases (hazard ratio 2.5; 95% CI 1.4-4.3, p=0.002), and a more advanced WHO-performance score (hazard ratio 1.8; 95% CI 1.4-2.3, $p<0.001$) correlated with a shorter survival.

Table 1: Clinical characteristics of 95 patients with inoperable esophageal carcinoma treated with single dose brachytherapy

Characteristic	
Age (years ± SD)	69 ± 13
Gender M/F	71/24
Tumor histology (N (%))	
Squamous cell carcinoma	27 (28)
Adenocarcinoma	65 (68)
Other	3 (3)
Tumor length (mean ± SD)	7.4 ± 2.6
< 10 cm (N (%))	68 (72)
≥ 10 cm (N (%))	27 (28)
Location of tumor (N (%))	
Esophagus	82 (86)
Cardia	13 (14)
Indication for palliative treatment (N (%))	
Metastases	63 (66)
Poor general condition	21 (22)
Both	11 (12)
Dysphagia score before treatment (N (%))	
2	40 (42)
3	36 (38)
4	19 (20)
WHO performance score (scale 0-4) (mean ± SD)	1.0 ± 1.0
Dilation before treatment (N (%))	23 (24)
Previous chemotherapy treatment (N (%))	12 (13)

Persistent dysphagia

Eighteen (19%) of 95 patients reported persistent dysphagia within 4 weeks after treatment. In these patients, endoscopy confirmed persistent tumor growth. These patients were treated with a metal stent. Univariable logistic regression analysis showed that a dysphagia score of 4 (complete obstruction) before treatment, dilation prior to treatment, and previous chemotherapy treatment increased the risk of persistent dysphagia (Table 2). In a multivariable analysis, dilation prior to treatment proved to be the most important factor for the risk of persistent dysphagia. There was a trend towards a higher risk for persistent dysphagia in patients previously treated with chemotherapy (Table 3).

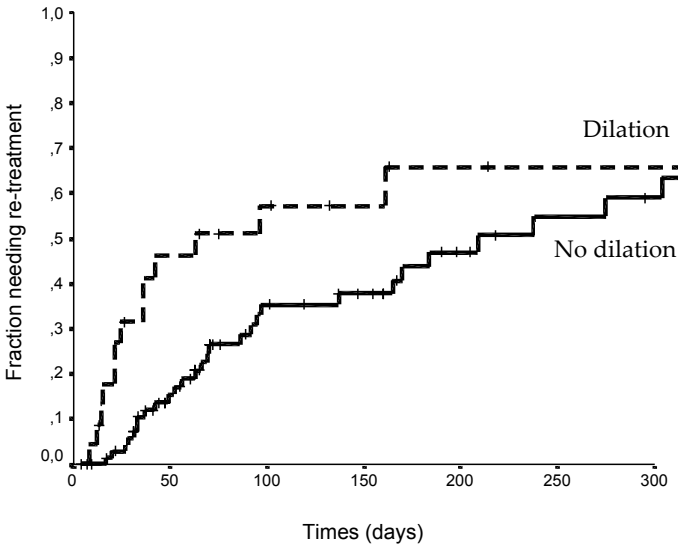
Table 2: Univariable Cox and logistic analysis of variables on the risk of persistent (n=18) or persistent and recurrent dysphagia (n=42) after single dose brachytherapy (n=95). The univariable Cox analysis for recurrent dysphagia (n=28) is not shown as none of the variables evaluated were associated with an increased risk.

Variable		Logistic regression persistent dysphagia			Cox regression total persistent and recurrent dysphagia		
	N	Events	Odds Ratio (95% CI)	p-value	Events	Hazard Ratio (95% CI)	p-value
Age	95	18	0.97 (0.94-1.02)	>0.20	42	0.99 (0.97-1.02)	>0.20
Gender							
Male	71	11	1.0	0.15	31	1.0	>0.20
Female	24	7	2.2 (0.76-6.7)		11	1.3 (0.6-2.5)	
Tumor histology							
Squamous cell carc / other	30	6	1.0	>0.20	14	1.0	>0.20
Adenocarcinoom	65	12	0.9 (0.3-2.7)		28	1.01 (0.5-1.9)	
Tumor length							
<10cm	68	13	1.0	>0.20	31	1.0	>0.20
≥10cm	27	5	0.96 (0.3-3.0)		11	1.2 (0.6-2.4)	
Location of tumor							
Esophagus	82	15	1.0	>0.20	34	1.0	>0.20
Esophagogastric junction	13	3	1.3 (0.3-5.5)		8	1.2 (0.5-2.5)	
Metastases							
No	21	2	1.0	>0.20	8	1.0	0.19
Yes	74	16	2.6 (0.6-13)		34	1.7 (0.8-3.7)	
Unfit to undergo curative therapy							
No	63	15	1.0	0.10	32	1.0	0.06
Yes	32	3	0.33 (0.09-1.2)		10	0.5 (0.3-1.02)	
Dysphagia score before treatment							
<4	76	11	1.0	0.03	32	1.0	0.09
4	19	7	3.4 (1.1-11)		10	1.9 (0.9-3.8)	
WHO performance score							
0	33	6	0.82 (0.5-1.4)	>0.20	19	0.9 (0.6-1.2)	>0.20
1	36	9			17		
2	16	2			4		
3 / 4	10	1			2		
Dilation before treatment							
No	72	9	1.0	0.007	29	1.0	0.045
Yes	23	9	4.5 (1.5-13)		13	2.0 (1.02-3.8)	
Previous chemotherapy treatment							
No	83	13	1.0	0.04	36	1.0	0.17
Yes	12	5	3.8 (1.1-14)		6	1.8 (0.8-4.4)	
Total	95	18			42		

Table 3: Multivariable logistic and Cox regression model of variables associated with the risk of persistent dysphagia (n=18) or persistent and/or recurrent dysphagia (n=42) after single dose brachytherapy (n=95). Variables were selected in a backward stepwise procedure with p<0.20. The separate model for recurrent dysphagia (n=28) did not been show any variable to be significant.

Variable	Logistic regression persistent dysphagia		Cox regression total persistent and recurrent dysphagia	
	Odds ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Dilation before treatment	4.1 (1.3-12)	0.01	2.1 (1.1-4.1)	0.03
Previous chemotherapy treatment	3.2 (0.81-12)	0.097	-	-

Figure 1: Effect of dilation before treatment on the risk of persistent or recurrent dysphagia in patients with esophageal carcinoma after single dose brachytherapy (n=95).



Recurrent dysphagia

In total, 34 events of recurrent dysphagia occurred in 28/95 (29%) patients. Recurrent dysphagia was caused by tumor regrowth (n=26), food bolus obstruction (n=5), stent migration (n=2), and oblique stent positioning (n=1). Tumor regrowth was treated by placement of a metal stent (19/26; 73%), a second dose of brachytherapy (3/26; 12%) or another treatment (4/26; 15%). Stent migration and oblique stent positioning occurred in 3 patients after stent placement for tumor regrowth after initial brachytherapy. Univariable and multivariable Cox regression analysis showed that none of the investigated patient and tumor characteristics were associated with an increased risk of recurrent dysphagia.

Persistent and/or recurrent dysphagia

In total, 42/95 (44%) patients needed additional treatment due to persistent and/or recurrent dysphagia after single dose brachytherapy. Both univariable and multivariable Cox regression analysis showed that dilation prior to treatment increased the risk of additional treatment for persistent and/or recurrent dysphagia after single dose brachytherapy (Figure 3).

DISCUSSION

Single dose brachytherapy is an effective treatment for the palliation of dysphagia from esophageal cancer, however both persistent and recurrent dysphagia diminish its effectiveness both on the short and long term after treatment. This will negatively influence quality of life in this group of patients with only a limited life expectancy. We found that dilation prior to treatment was a risk factor for persistent and recurrent dysphagia after single dose brachytherapy. In addition, there was a trend towards a higher risk for persistent dysphagia in patients previously treated with chemotherapy.

Patients which stenotic tumors that needed dilation to pass the applicator down the esophagus had a higher risk of persistent and recurrent dysphagia. This can probably be explained by the larger tumor load in these patients, resulting in only a partial effect of the radiation on the tumor. The radiation dose of 12 Gy was administered at 1 cm from the source axis of the applicator. This means that the dose administrated to the surface of the tumor (0.5 cm from the source axis) amounted 200% of the prescribed dose. The dose at 1.25 cm from the source axis (at 0.75 cm from the surface of the tumor) amounted only 65%. A single dose of 12 Gy brachytherapy was probably less or not effective for these patients with a large

tumor load (18). Increasing the dose is likely to improve the results of brachytherapy for these patients. Moreover, it has recently been shown that it is best to deliver this higher dose in two or three fractions to prevent serious radiation complications (14, 19).

There was a trend towards patients with previous chemotherapy treatment having a higher risk of persistent dysphagia after treatment with brachytherapy. Chemotherapy consisted of a combined treatment of cisplatin and paclitaxel (n=9), or carboplatin and paclitaxel (n=3) with a median of 6 doses given to each patient. In general, it has been reported that the results of chemotherapy before radiotherapy are disappointing, whereas concurrent radiation and chemotherapy leads to a better therapeutic effect (20, 21). The mechanism(s) that decrease the effect of radiation therapy after chemotherapy are not fully understood. Chemotherapy may lead to cell death and fibrosis, which will decrease the blood supply and thereby the delivery of oxygen to the tumor. Much of the tissue damage from radiation therapy depends on the formation of free radicals resulting in DNA damage (22). Since this process requires oxygen, it seems likely that a decreased oxygen supply in tumors after chemotherapy is an important factor in determining resistance to radiation therapy. In addition, there might be a higher probability of selection of drug-resistant cells that may be cross-resistant to radiation therapy (21).

In the consensus guideline of the American Brachytherapy Society, several tumor characteristics have been distinguished to divide patients in good and poor candidates, and patients with contraindications for brachytherapy (13). These guidelines were established for brachytherapy in combination with external beam radiation for the definitive and palliative treatment of esophageal cancer. In the present study, we focused on single dose brachytherapy as a palliative treatment modality for esophageal cancer. Contraindications for brachytherapy described by the American Brachytherapy Society include an esophageal fistula and a cervical esophageal location of the tumor. These patients were excluded in our study. A third contraindication in the guidelines is a stenotic tumor that cannot be bypassed. In this study, patients with a stenotic tumor underwent dilation on the day of brachytherapy. Dilation of the tumor did not increase the risk of developing major complications, such as perforation or hemorrhage ($p>0.20$). We confirmed however, that these patients had an increased risk of persistent and recurrent dysphagia. Poor candidates described by the American Brachytherapy Society are patients with a tumor length of more than 10 cm, tumors involving the gastroesophageal junction or cardia, extra-esophageal extension of the tumor, and regional lymphadenopathy (13). In the present study, patients were selected with inoperable cancer of the

esophagus or esophagogastric junction due to metastatic disease and/or a poor medical condition. In our experience of 95 patients treated with brachytherapy, tumor lengths of 10 cm or more, tumors involving the gastroesophageal junction, or metastatic disease did not increase the risk of additional treatment for persistent or recurrent tumor growth. Multivariable Cox regression analysis showed however that a tumor length of 10 cm or more and the presence of metastases correlated with a shorter survival. Based on our results, it is our opinion that patients with a long tumor (≥ 10 cm), a tumor involving the gastroesophageal junction, or metastatic disease can effectively be palliated for dysphagia with single dose brachytherapy.

Which palliative treatment could be an alternative for patients who are poor candidates for single dose brachytherapy? Stent placement is presently a commonly used and effective palliative treatment modality for dysphagia from esophageal cancer. For patients with stenotic tumors that cannot be bypassed, stent placement should be an attractive alternative since stent placement offers a more rapid relief of dysphagia (16). We recently demonstrated that metal stent placement is a safe and effective palliative treatment for malignant dysphagia in patients who underwent prior radiation and/or chemotherapy (23).

Our findings can be used to establish a more individualized palliative treatment strategy for patients with dysphagia from esophageal cancer. Patients with a tumor size of more than 10 cm, a tumor located across the gastroesophageal junction or with evidence of metastatic disease can effectively be palliated with single dose brachytherapy. Patients with stenotic tumors that cannot easily be bypassed or previously underwent chemotherapy are poor candidates for single dose brachytherapy. For these patients alternative palliative treatment modalities, such as stent placement, should be considered.

APPENDIX

The Dutch SIREC study group consisted of:

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Mulder, Peter J. Wahab; Arnhem Radiotherapeutic Institute: Janny G. Reinders. *The Netherlands Cancer Institute, Amsterdam:* Dept. of Gastroenterology: Henk Boot; Dept. of Radiotherapy Berthe M.P. Aleman. *Leyenburg Hospital, The Hague:* Dept. of Gastroenterology: Jan J. Nicolai; Dept. of Radiotherapy: Frank M. Gescher. *Medical Centre Haaglanden, The Hague:* Dept. of Internal Medicine: Maarten A.C. Meijssen; Dept. of Radiotherapy: Ruud G.J. Wiggenraad. *Gelre Hospital, Apeldoorn:* Dept. of Internal Medicine Jitty M. Smit. *Reinier de Graaf Hospital, Delft:* Dept. of Gastroenterology: Clemens J.M. Bolwerk.

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5

Stent placement

5A

Prior radiation and/or chemotherapy has no effect on the outcome of metal stent placement for esophagogastric carcinoma

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ABSTRACT

Objective: It is still unclear whether prior radiation and/or chemotherapy (RTCT) increases the risk of complications after self-expanding metal stent placement in patients with inoperable esophagogastric carcinoma. We evaluated the influence of prior RTCT on the outcome of stent placement in a large group of patients.

Methods: From October 1994 to December 2000, 200 patients underwent self-expanding metal stent placement for malignant dysphagia, and were followed prospectively. Forty-nine of these patients had received prior RTCT (chemotherapy n=35, radiation therapy n=8, or both n=6).

Results: At 4 weeks after stenting, the dysphagia score had improved similarly in patients with or without prior RTCT, from a median of 3 to 0 ($p<0.001$). The occurrence of major complications (bleeding, perforation, fistula formation, fever and severe pain) was not different between patients with or without prior RTCT (29% versus 21%; relative risk (RR)=1.15 (95% CI 0.54-2.46; p=0.72)), as was the occurrence of recurrent dysphagia due to tumor overgrowth, stent migration, or food-bolus impaction (35% versus 27%; RR=1.49 (95% CI 0.71-3.13; p=0.29)). Median survival of both patient groups after stent placement was similar (110 versus 93 days; RR=0.90 (95% CI 0.60-1.34; p=0.60) for prior RTCT versus no prior treatment). Only minor complications (mainly mild retrosternal pain) occurred more frequently in patients with prior RTCT (41% versus 15%; RR=2.12 (95% CI 1.06-4.25; p=0.035)).

Conclusions: Both the incidence of life-threatening complications and survival after self-expanding metal stent placement for esophagogastric carcinoma are not affected by prior RTCT, however retrosternal pain occurs more frequently in patients who had previously undergone RTCT.

INTRODUCTION

More than 50% of patients with carcinoma of the esophagus or the gastric cardia have inoperable disease at presentation and most of them require palliative treatment to relieve progressive dysphagia. At present, self expanding metal stent placement is a commonly used method for the palliation of malignant dysphagia. Previously reported studies have demonstrated that stent placement is an effective and safe method for palliation of malignant dysphagia (1-9). An unresolved question is whether prior radiation and/or chemotherapy (RTCT) affects the outcome. Eight studies addressed this question (1, 6, 10-15) (Table 1).

Table 1: Overview of studies on the influence of prior radiation and/or chemotherapy on the outcome of stent placement for palliation of esophagogastric carcinoma.

Author / Year (ref.)	No. of patients	Type of study	Type of stent	Life-threatening complications
Increased risk				
Bethge et al. 1996 (14)	Prior RTCT: n=13 Prior surgery: n=4 No controls	Prospective	Wall stent	3/17 (18%)
Kinsman et al. 1996 (10)	Prior RTCT: n=22 No treatment: n=37	Retrospective	Z-stent	8/22 (36%) 1/37 (3%)
Siersema et al. 1998 (6)	Prior RTCT: n=28 No treatment: n=47	Prospective	Plastic tubes n=38 Z-stent n=37	12/28 (43%) 8/47 (17%)
Muto et al. 2001(15)	Prior RTCT: n=13 No controls	Retrospective	Ultraflex n=9 Wall stent n=2 Z-stent n=2	7/13 (54%)
No difference				
Kozarek et al. 1996 (11)	Prior RTCT: n=59 No treatment: n=26	Retrospective	Plastic tubes n=47 Z-stent n=26 Wall stent n=10 Esophacoil/Ultraflex n=2	Tubes: 2/32 (6%) vs. 1/15 (7%) SEMS: 1/27 (4%) vs. 1/11 (9%)
Nelson et al. 1997 (12)	Prior RTCT: n=6 No/other treatment: n=15	Retrospective	Wall stent	0/6 (0%) ?
Raijman et al. 1997 (13)	Prior RTCT: n=39 No treatment: n=21	Retrospective	Wall stent	3/39 (8%) 2/21 (10%)
Bartelsman et al. 2000 (1)	Prior RTCT: n=54 No treatment: n=99	Retrospective	Song stent	No relation (not further specified)
Present series	Prior RTCT: n=49 No treatment: n=151	Prospective	Z-stent n=70 Wall stent n=71 Ultraflex stent n=59	14/49 (29%) 31/151 (21%)

Four studies showed an increased risk of complications after prior RTCT (6, 10, 14, 15), whereas the other four studies did not find such a relationship (1, 11-13). Sample sizes of these studies were rather small, six studies were retrospective (1, 10-13, 15), and two studies also included conventional prosthesis (6, 11).
In this study, data of all patients who underwent self-expanding metal stent placement for palliation of malignant dysphagia performed in our hospital were combined, which resulted in 200 prospectively followed patients. We investigated whether prior RTCT influenced functional outcome, complication rate, the occurrence of recurrent dysphagia and survival after stent placement.

METHODS

From October 1994 to December 2000, 200 patients with dysphagia caused by an inoperable carcinoma of the esophagus or gastric cardia, or recurrent dysphagia after prior radiation with curative or palliative intent for esophageal cancer were palliated with a self-expanding metal stent in the Erasmus MC Rotterdam.

Three types of metal stents were inserted: the covered Gianturco-Z stent (Wilson-Cook Europe A/S, Bjaeverskov, Denmark), the partially covered Flamingo Wallstent (Microvasive/Boston Scientific Corp., Watertown, Mass., USA), and the partially covered Ultraflex stent (Microvasive/ Boston Scientific Corp., Watertown, Mass., USA). If it was impossible to pass the tumor with an endoscope, the stricture was dilated to 9-14 mm by a KeyMed Advanced Esophageal Dilator (KeyMed Ltd., Southend-on-Sea, U.K.). The proximal and distal tumor margins were marked by injecting radiographic contrast medium into the submucosa through a sclerotherapy needle. The stent was introduced and deployed under fluoroscopic monitoring. The stent was at least 2-4 cm longer than the stricture to allow for a 1-2 cm extension above and below the proximal and distal tumor margins. Following placement, deployment of the stent was endoscopically and radiographically assessed. All patients were consciously sedated with midazolam (Dormicum^{R}, Roche Nederland BV, Mijdrecht, the Netherlands). Written informed consent was obtained from all patients.

All patients were evaluated before stent placement and at 4-week intervals until death. Regular follow-up visits were made by a specially trained nurse and/or by telephone calls to the patient's general practitioner. If indicated, patients were readmitted for clinical evaluation. Dysphagia was scored before treatment and at 4 weeks after stent placement, according to Ogilvie et al. (16) as: grade 0: ability to eat

a normal diet; grade 1: ability to eat some solid food; grade 2: ability to eat some semisolids only; grade 3: ability to swallow liquids only; grade 4: complete dysphagia. Major complications were defined as life-threatening or severe complications, such as perforation, bleeding, fever, fistula formation and severe pain, whereas minor complications were defined as not life-threatening or moderately severe complications such as mild retrosternal pain and gastroesophageal reflux. Pain was defined as mild pain if it was treatable with non-narcotic analgesics, such as acetaminophen or a non-steroidal anti-inflammatory drug, or (low-dose) narcotic analgesics for a period of maximal 3 days. Severe pain was pain for which (high-dose) narcotic analgesics for a longer period and/or removal of the stent was indicated. Early complications were defined as procedure-related complications occurring within 7 days after stent placement. Complications occurring more than 7 days after treatment, for which it was often unsure whether these were related to placement of the stent or progression of the disease, were defined as late complications.

The results were expressed as means ± standard deviation (SD), dysphagia scores were expressed as medians. The improvement of the dysphagia score was analyzed using Wilcoxon signed-ranks test, and differences in dysphagia score improvement between the patient group with prior RTCT and the group without prior treatment was determined by the Mann-Whitney test. The observed median survival was calculated using the Kaplan Meier method. Multivariate Cox regression analysis was performed to investigate differences in the occurrence of major and minor complications, recurrent dysphagia, and survival between the group with prior RTCT and the group without prior treatment. Covariates included in the analysis were gender, age, histology, length and location of the tumor, type, length and diameter of stent, and dilation before stent placement. Age and histology were always included in the different models because of a skew distribution of age and a difference in the incidence of squamous cell carcinoma and adenocarcinoma between the prior RTCT group and the group without prior treatment. Interactions between covariates, particularly prior RTCT / no prior RTCT with age and tumor histology were tested. The assumption of proportional hazards of the Cox regression was tested for each covariate extending the model with covariate*log (follow-up time). The used level of significance was α=0.05.

RESULTS

Clinical characteristics

The clinical characteristics of the two patient groups are shown in table 2. Forty-nine patients had received prior chemotherapy (n=35), prior radiation therapy (n=8) or both (n=6). Chemotherapy consisted of the combination Cisplatinum and Paclitaxel (n=31), or the combination Cisplatinum, 5FU and Vepesid (n=10) with a median of 5 (range 1-8) treatments. The median total radiation dose was 30 (range 15-66) Gy, including five patients receiving external beam radiation with additional intraluminal radiotherapy (brachytherapy). The median time between the end of the radiation and/or chemotherapeutic treatment and stent placement was 64 (range 6-899) days.

Outcome of stent placement

Successful placement of a self-expanding metal stent was achieved in 198 (99%) of the 200 patients (Table 3). For one stent the releasing system failed and another stent migrated during placement. Both these stents were removed and a second metal stent was successfully inserted.

Table 2: Clinical characteristics of 200 patients with or without prior radiation and/or chemotherapy (RTCT) given a self expanding metal stent for palliation of malignant dysphagia

	Prior RTCT (n=49)	No prior RTCT (n=151)
Mean Age (y)*	60±11	72±11
Gender (%)		
Male	37 (75)	113 (75)
Female	12 (25)	38 (25)
Tumor histology (%)†		
Squamous cell carcinoma	22 (45)	44 (29)
Adenocarcinoma	25 (51)	103 (69)
Other	1 (2)	2 (1)
Unknown	1 (2)	2 (1)
Mean Tumor length (cm)	7.8±2.5	7.7±2.5
Type of stent (%)		
Ultraflex stent	12 (24)	47 (31)
Flamingo Wall stent	18 (37)	53 (35)
Gianturco-Z stent	19 (39)	51 (34)
Dilation before stent placement	9 (18)	13 (9)

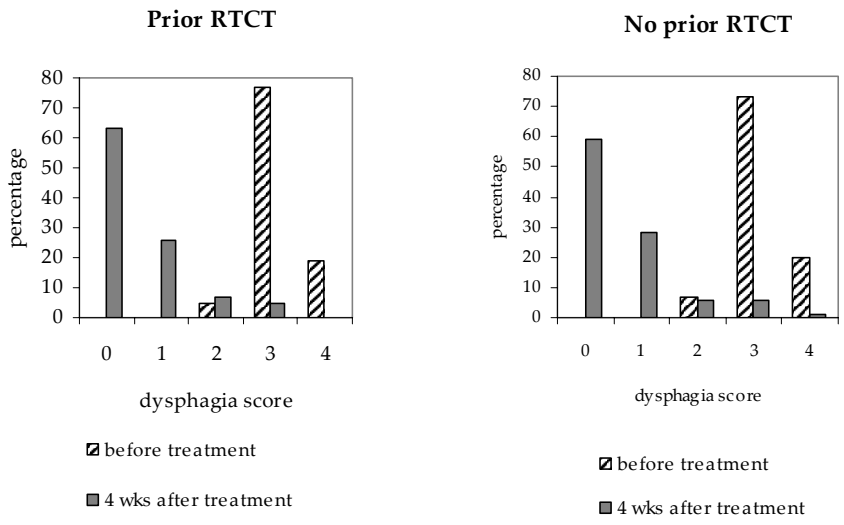
*p=0.02
†p=0.03

Table 3: Outcome and survival in 200 patients with or without prior radiation and/or chemotherapy (RTCT) given a self-expanding metal stent for palliation of malignant dysphagia

	Prior RTCT (n=49)	No prior RTCT (n=151)
Technical success (%)	48 (98)	150 (99)
Median dysphagia score before stent placement* (10^e – 90^e percentile)	3 (3-4)	3 (3-4)
Median dysphagia score at 4 weeks after stent placement* (10^e – 90^e percentile)	0 (0-2)	0 (0-2)
30-day mortality (%)	7 (14)	24 (16)
Median survival in days (95% CI)	110 (62-158)	93 (77-109)

* on a scale from 0 (normal) to 4 (complete dysphagia)

Figure 1: Dysphagia scores (on a scale from 0 (normal) to 4 (complete dysphagia)) in patients with (n=43) or without (n=128) prior radiation and/or chemotherapy (RTCT) before and 4 weeks after stent placement for palliation of malignant dysphagia.



At 4 weeks after stenting, the dysphagia score had improved from a median of 3 to 0 ($p<0.001$) in both groups (Figure 1). There was no difference in the degree of improvement between both groups. The dysphagia score at 4 weeks had improved in 161/171 (94%) of the patients by at least one grade, allowing an equal number of patients to eat solids or semi-solids, 27 patients died before the 4 weeks follow-up, and for 2 patients data were missing.

Major complications

Multivariate Cox regression analysis showed that the occurrence of major (both early and late) complications did not differ between both groups (Table 4). The relative risk (RR) for a major complication was RR=1.15 (95% confidence interval (CI) 0.54-2.46; p=0.72) for patients with prior RTCT versus no prior treatment.
Early major (procedure-related) complications occurred in 3 (6%) patients who underwent prior RTCT and in 13 (9%) patients without prior treatment (Table 5). The relative risk for a major complication within 7 days after stent placement was RR=0.70 (95% CI 0.19-2.60; p=0.58) for patients with prior RTCT versus no prior treatment. One patient who had previously received chemotherapy experienced severe pain during placement of a metal stent. The stent was removed and a feeding tube was placed. Two patients, both treated with chemotherapy, developed fever within 24 hours after placement of a metal stent. These patients were not neutropenic and a chest X-ray showed no evidence of perforation or aspiration pneumonia. Both patients recovered after treatment with antibiotics and feeding through a naso-duodenal tube. In the group with no prior treatment, nine perforations occurred, two of these were fatal (see below), while seven patients improved with conservative treatment, later dying of causes unrelated to the perforation. One patient developed hematemesis within 24 hours after placement and required a transfusion. One patient developed fever without evidence of a perforation or aspiration, and this was treated with antibiotics. Two patients experienced severe pain in the first week following stent placement. In one of these patients, removal of the stent resulted in diminution of the pain. Subsequently, this patient was treated by radiation therapy. An endoscopy in the other patient revealed an ulcer at the proximal end of the stent, which was treated by retraction of the stent.

Table 4: Relative Risk (RR) for a major complication, minor complication, recurrent dysphagia and survival for patients with prior RTCT versus no prior RTCT according to a multivariate Cox regression analysis

	RR (Prior RTCT versus No Prior RTCT) (95% CI)	p-value
Major complications	1.15 (0.54-2.46)	p=ns
≤ 7 days	0.70 (0.19-2.60)	p=ns
> 7 days	1.46 (0.61-3.53)	p=ns
Minor complications	2.12 (1.06-4.25)	p=0.035*
Recurrent dysphagia	1.49 (0.71-3.13)	p=ns
Survival	0.90 (0.60-1.34)	p=ns

Table 5: Complications and recurrent dysphagia in 200 patients with or without prior radiation and/or chemotherapy (RTCT) after placement of a self-expanding metal stent for palliation of esophagogastric cancer

	Prior RTCT (n=49)	No prior RTCT (n=151)
Major complications	15 in 14 patients (29%)	33 in 31 patients (21%)
≤ 7 days		
Perforation		9
Bleeding		1
Fever	2	1
Severe pain	1	2
> 7 days		
Bleeding	11	17
Fistula		2
Severe pain	1	1
Minor complications*	24 in 20 patients (41%)	24 in 22 patients (15%)
Retrosternal pain	15	14
Gastroesophageal reflux	8	10
Atrial Fibrillation	1	
Recurrent dysphagia	21 in 17 patients (35%)	46 in 40 patients (27%)
Tumor overgrowth	12	15
Migration of device	5	19
Food-bolus impaction	4	11
Fracture of device		1

*p=0.035

Late major complications, including hematemesis, fistula formation and severe pain, occurred in 12 (24%) patients with prior RTCT and in 20 (13%) patients without prior treatment (Table 5). The relative risk for a major complication occurring more than 7 days after treatment was RR=1.46 (95% CI 0.61-3.53; p=0.40) (Table 4) for patients with prior RTCT versus no prior treatment. Eleven patients who were treated with prior RTCT developed hematemesis after a median of 59 days (range 8-260 days). One patient who received prior chemotherapy complained of severe pain 2 months after stent placement and insisted on removal of the stent. Endoscopy showed tumor progression after stent removal. This patient was then treated with brachytherapy without improvement of dysphagia and finally received a PEG-catheter. In the group of patients without prior RTCT, 17 patients developed hematemesis after a median of 41 days (range 8-510 days). Two patients developed an esophagorespiratory fistula at 2 months and 6.5 months, respectively. In both patients this was treated with a second covered metal stent. One patient experienced severe pain at 10 days after stent placement due to pressure necrosis at the proximal end of the stent. The stent was retracted over 2 cm, resulting in disappearance of the pain.
Dilation before stent placement, particularly in the group with prior treatment (9/49 (18%) vs. 13/151 (9%) in patients without prior treatment; p=0.06), significantly increased the risk of major complications compared to patients without prior dilation (p=0.03). Five of the nine perforations occurred in patients, in whom the stricture was dilated before stent placement. Interactions with prior RTCT / no prior RTCT were not significant.

Minor complications

Minor complications occurred more frequently in patients who underwent prior RTCT (prior RTCT: 41% versus no prior RTCT: 15%, Table 5). The relative risk for a minor complication was RR=2.12 (95% CI 1.06-4.25; p=0.035) for patients with prior RTCT versus no prior treatment (Table 4). Minor retrosternal pain was observed in 15 (31%) patients with prior RTCT compared to 14 (7%) patients without prior treatment. Eight patients with prior RTCT and 10 patients without prior treatment experienced symptoms of gastroesophageal reflux, which was treated with a proton-pump inhibitor.

Recurrent dysphagia

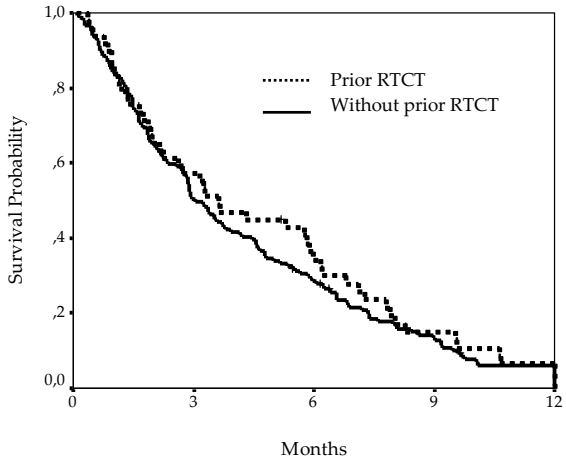
Sixty-seven incidents of recurrent dysphagia occurred in 57 patients, at a similar rate in both groups, and this was caused by tumor overgrowth (n=27), stent migration (n=24), food bolus-impaction (n=15) and fracture of the stent (n=1) (Table 5). Eight patients had two episodes of recurrent dysphagia with a different cause and one patient had three episodes of dysphagia with a different cause. The relative risk for recurrent dysphagia was RR=1.49 (95% CI 0.71-3.13; p=0.29) for patients with prior RTCT versus no prior treatment, after correction for stent length (Table 4). Length of stent was also included in the analysis because there was a trend (p=0.07) that a longer stent length was associated with an increased risk of developing recurrent dysphagia.

Recurrent dysphagia due to tumor overgrowth at the proximal or distal end of the stent occurred in 12 patients who were previously treated with RTCT after a median of 116 days (range 33-290), and in 15 patients without prior treatment after a median of 125 days (range 26-364 days). Stent migration occurred in 5 patients with prior RTCT after a median of 18 days (range 5-147 days), and in 19 patients without prior treatment after a median of 57 days (range 0-399 days). One patient had two incidents of food-bolus impaction within one week, occurring almost 6 months after placement of the stent, and it was found to be caused by a fracture of the stent.

Survival

Median survival of all patients was 99 days, with no statistically significantly difference between both groups (Table 3, Figure 2). The relative risk was 0.90 (95% CI 0.60-1.34; p=0.60) for patients with prior RTCT versus no prior treatment (Table 4). Stent-related mortality was 2% (1 patient) in the group with prior RTCT and 1% (2 patients) in the group without prior treatment. One patient, previously treated with chemotherapy, developed fatal hematemesis 18 days after stent placement. At autopsy, one of the edges of the proximal end of the stent had perforated the esophageal wall, leading to a fistula between the esophagus and aorta (17). In the group with no prior treatment, 2 patients died from septic complications following perforation after stent placement. The majority (74%) of the other patients died from tumor progression, whereas 12% of patients died from causes unrelated to the tumor. Eleven patients died from hematemesis for which it was uncertain whether this was due to tumor progression, stent placement or another etiology, because no endoscopy or autopsy were performed in these patients. In 9 patients the cause of death was unknown, 2 patients were lost to follow-up, and 4 patients are still alive.

Figure 2: Kaplan-Meier plots showing no significant difference in survival between patients with and without prior radiation and/or chemotherapy (RTCT) (0 months indicates the day of stent placement).



DISCUSSION

The influence of prior RTCT on the outcome of self-expanding metal stent placement is as yet still unresolved. In this study, the occurrence of major complications and survival after stent placement were similar for patients with or without prior RTCT. This is in contrast with our previous published conclusion that prior RTCT indeed increases the risk of device-related complications (6) (Table 1). It was drawn from a study comparing placement of conventional prosthesis with self-expanding metal stents. The majority of complications occurred in patients with conventional prostheses. The present study involved only patients, who were treated with a self-expanding metal stent.

The most optimal method to investigate the effect of prior RTCT on the occurrence of complications after stent placement would be to perform a randomized trial. Randomized studies comparing palliative radiation and/or chemotherapy with no treatment are however rare (18, 19), and for an ideal study all patients from both groups (RTCT and no treatment) should undergo stent placement after a defined period. This is practically not feasible, as patients will only be treated with a stent if they develop dysphagia at some stage. In addition, if patients with inoperable esophagogastric carcinoma are offered the option of radiation and/or chemotherapy, they are often not willing to be randomized. Therefore, in our opinion, this study with a large number of patients (n=200) and prospectively collected data offers the

best possibility to study the influence of prior RTCT on the outcome of metal stent placement.

A retrospective study by Kinsman et al. (10) in 59 patients with obstructive esophagogastric carcinoma also showed an increased risk of life-threatening complications, including hematemesis, perforation or fistula formation, after placement of a Gianturco-Z stent in patients treated with prior RTCT compared to patients without prior treatment (8/22 (36%) versus 1/37 (3%); p=0.012). Bethge et al. (14) prospectively followed 17 patients with prior curative RTCT (n=13) or surgery (n=4) treated with a Wallstent for recurrent dysphagia. During follow-up, there were 3 fatal complications (aortoesophageal fistula in 1 patient after 137 days, and septic complications in 2 patients at 39 and 52 days after stenting). Muto et al. (15) retrospectively analyzed the results of stent placement in 13 patients after failure of primary chemoradiotherapy. Perforation occurred in 3 (23%) patients, stent-related mediastinitis and pneumonia developed in 6 (46%) and 3 (23%) patients, respectively. Seven (54%) patients died from pulmonary complications. In the last two cited studies, no patients without prior RTCT were included (14, 15).

Four retrospective studies support the results of the present study in demonstrating no difference in life-threatening or device-related complications after self-expanding metal stent placement between patients with prior RTCT and patients without prior treatment. Raijman et al. (13) analyzed the data of 60 patients, treated with a Wallstent for malignant dysphagia or an esophagorespiratory fistula. Life-threatening complications, defined as bleeding requiring blood transfusion, perforation, fistula formation, or aspiration pneumonia, occurred in 3 (8%) of 39 patients with prior RTCT and in 2 (10%) of 21 patients without prior treatment. Nelson et al. (12) studying 23 patients treated with a Wallstent for inoperable malignant esophagogastric carcinoma, found that none of the 6 patients with prior radiotherapy and chemotherapy experienced life-threatening complications, such as perforation or bleeding within the first week after stent placement. Bartelsman et al. (1) evaluated the outcome of Gianturco-Z stents in 153 patients with esophagogastric malignancies. They also failed to identify any relationship between previously RTCT (35% of the patients) and the occurrence of device-related complication (not further specified). Finally, Kozarek et al. (11), comparing placement of conventional prosthesis and self-expanding metal stents for inoperable esophageal carcinoma, found no association between prior RTCT and the development of stent-related complications, such as stent erosion with consequent tracheoesophageal fistulas or bleeding in the esophagus. In patients treated with a

self-expanding metal stent, 1 of 27 (4%) patients previously treated with RTCT had such a complication, against 1 of 11 (9%) patients without prior treatment.

In some respects the two groups in our study were not wholly comparable. The median age of the patients with prior RTCT was significantly lower compared to the group without prior treatment. This reflects the fact that younger patients are more often considered suitable candidates for radiation and/or chemotherapy. A histological diagnosis of squamous cell carcinoma was observed more often in the group with prior RTCT, which was due to the fact that some of these patients participated in a trial, studying the effect of chemotherapy on squamous cell carcinoma. For this reason a multivariate analysis was performed, to correct for these differences between the groups. We want to emphasize that in none of the studied endpoints (major and minor complications, recurrent dysphagia, and survival) age and histology had a significant influence.

Dilation prior to stent placement was a risk factor for perforation, independent from the fact whether prior radiation and/or chemotherapy had been administered. Some authors advocate a gradual dilation of the stricture over several sessions before stent placement (3, 20). It is, however, questionable whether the increased risk of perforation is due to the dilation itself and it may well be inherent to the tightness of the malignant stricture. Recently, a method was described for the placement of metal stents under fluoroscopic control, making dilation unnecessary, and allowing the small caliber delivery system of self-expanding metal stents to be negotiated through malignant esophageal strictures (21). Although this method seems promising, further studies are needed to establish whether the occurrence of major complications such as perforation can be reduced by this method.

Minor complications were more common in patients with prior RTCT, particularly retrosternal pain (31% versus 7%). This is possibly due to therapy effects of radiation and chemotherapy such as necrosis and fibrosis, resulting in the esophageal wall being more prone to develop pain (22). Chest pain after placement of a self-expanding metal stent is in itself a common problem. In a study by Golder et al. (23), 26/52 (50%) patients required narcotic analgesics for chest pain within 48 h after stent placement compared to 11/52 (21%) before stenting. Adequate pain control after stenting is therefore indicated, especially for patients with prior RTCT.

The incidence of recurrent dysphagia was not significantly different between patients with or without prior RTCT. The observed trend of more recurrent dysphagia for a longer stent length needs to be verified in further studies. However, as yet, there is no plausible reason that could explain this observation.

In conclusion, our results indicate that prior RTCT does not increase the risk of major complications after stent placement, compared to patients without prior treatment. Stent placement was effective in relieving dysphagia, at a similar rate in both groups. Only minor complications, particularly minor chest pain, occurred more often in the group with prior RTCT. The occurrence of recurrent dysphagia and survival rates were similar in both groups. Therefore, placement of a self-expanding metal stent is as safe and effective in patients with prior RTCT as in those without such treatment.

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5B

Causes and treatment of recurrent dysphagia after self-expanding metal stent placement for the palliation of esophageal carcinoma

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ABSTRACT

Background: Recurrent dysphagia frequently complicates the palliation of esophageal cancer with self-expanding metal stents. Neither the strategies nor the outcomes of re-interventions have been adequately reported.

Methods: Two-hundred sixteen patients underwent placement of a self-expanding metal stent (Ultraflex, n=75; Flamingo Wallstent, n=71; Z-stent, n=70) for malignant dysphagia, and were followed prospectively. The causes of stent-related recurrent dysphagia, the intervals after first stent placement, the procedures used for re-intervention and their outcomes were evaluated.

Results: Seventy-four episodes of stent-related recurrent dysphagia occurred in 63 (29%) patients, mainly due to tumor overgrowth (n=30; median: 129 days), stent migration (n=26; median: 92 days) and food bolus obstruction (n=16; median: 80 days). Stent migration occurred more frequently (p=0.05), whereas tumor overgrowth occurred less frequently (p=0.05) with Ultraflex stents compared to Flamingo Wallstents and Z-stents. Tumor overgrowth was treated in 25 patients mainly by a second stent (n=19) and was effective in 23/25 (92%) patients. Five patients received no further treatment**.** Stent migration was treated by placement of a second stent (n=14), repositioning of the migrated stent (n=7), other treatments (n=3), or no further treatment (n=2) and treatment was effective in 20/24 (83%) patients. Food bolus obstruction was treated by endoscopic stent clearance in all patients. Re-intervention for stent-related recurrent dysphagia improved the dysphagia score from a median of 3 to 1 ($p< 0.001$). Median survival after re-treatment was 68 days.

Conclusions: Recurrent dysphagia occurs in almost one-third of patients after stent placement. Re-intervention for stent-related recurrent dysphagia is effective in over 90% of patients. New innovations in stent design are needed to reduce the risk of stent-related recurrent dysphagia.

INTRODUCTION

The incidence of adenocarcinomas of the esophagus and esophagogastric junction is increasing at a faster rate than that of any other cancer (1-3). Self-expanding metal stents are now in common use for the palliation of cancer of the esophagus and gastro-esophageal junction. A number of studies have shown that self-expanding metal stent placement are both effective and safe for that purpose (4-10), however, the occurrence of recurrent dysphagia after stent placement remains the predominant problem during follow-up. The most frequently reported causes are stent-related problems, such as tumor overgrowth at the proximal or distal ends, stent migration and food bolus obstruction. Surprisingly little is known about the strategy and the outcome of re-intervention for stent-related recurrent dysphagia (11-13).

In the present study, involving a cohort of 216 prospectively followed patients after self-expanding metal stent placement, we investigated the incidence and the causes of stent-related recurrent dysphagia and, in addition, the procedures used for re-intervention, and their outcomes.

METHODS AND MATERIALS

Between October 1997 and July 2002, 216 consecutive patients with carcinomas of the esophagus or esophagogastric junction, which were non-resectable because of metastatic disease and/or a poor medical condition, were treated for dysphagia grade 2-4 on the dysphagia score (14) with a self-expanding metal stent and followed prospectively. Exclusion criteria were tumor growth within 3 cm of the upper esophageal sphincter, a fistula, previous self-expanding metal stent placement, WHO performance score of more than 3, or unfit to undergo conscious sedation. Clinical characteristics of the patient population are shown in Table 1. Written informed consent for prospective follow-up was obtained from all patients.

Three types of metal stents were used: 1) the partially covered Ultraflex stent (Microvasive/ Boston Scientific Corp., Watertown, Mass., USA) which is available in lengths of 10, 12 en 15 cm, and diameters of 18 mm or 22 mm at its midpoint; 2) the partially covered Flamingo Wallstent (Microvasive/Boston Scientific Corp., Watertown, Mass., USA), which is available in lengths of 12 cm (proximal diameter: 24 mm and distal diameter: 16 mm) and 14 cm (proximal diameter: 30 mm and distal diameter: 20 mm); and 3) the covered Z-stent (Wilson-Cook Europe A/S,

Bjaeverskov, Denmark), which is available in lengths of 10, 12 and 14 cm, and diameters of 18 mm or 22 mm at its midpoint (Table 1). Stent placement was performed according to a standardized procedure described previously (9).

Table 1: Clinical characteristics of 216 patients treated with a self expanding metal stent for the palliation of malignant dysphagia.

	Ultraflex N=75	**Flamingo Wall N= 71**	**Z stent N=70**
Mean age (years ± SD)	69 ± 12	69 ± 13	70 ± 11
Gender (M / F)	64 / 11	53 / 18	49 / 21
Tumor histology (N (%))			
Squamous cell carcinoma	27 (36)	25 (35)	19 (27)
Adenocarcinoma	48 (64)	43 (61)	50 (71)
Other / Unknown	-	3 (4)	1 (1)
Mean tumor length (cm ± SD)	8.0 ± 2.4	7.6 ± 2.4	7.8 ± 2.5
Location of tumor (N (%))			
Mid esophagus	15 (20)	14 (20)	12 (17)
Distal esophagus	46 (61)	38 (54)	38 (54)
Cardia	14 (19)	19 (27)	20 (29)
Indications for palliative therapy (N (%))			
Metastases	48 (64)	39 (55)	46 (66)
Local tumor progression	4 (5)	9 (13)	6 (9)
Poor medical condition	23 (31)	23 (32)	18 (26)
Length of stent (N (%))			
10	14 (19)	-	22 (31)
12	35 (47)	40 (56)[†]	22 (31)
14	-	31 (44)	-
15	26 (35)	-	26 (37)
Diameter of stent (N (%))			
Small (midpoint 18-20 mm)	66 (88)	40 (56) [†]	61 (87)
Wide (midpoint 22-25 mm)	9 (12)	31 (44)	9 (13)
Dilation before initial stent placement (N (%))	7 (9)	10 (14)	6 (9)
Initial dysphagia score (mean ± SD)	3.0 ± 0.7	3.2 ± 0.5	3.2 ± 0.5
Radiation and/or chemotherapy (N (%))			
Prior chemotherapy	16 (21)	16 (23)	14 (20)
Prior radiation	1 (1)	7 (10)	7 (10)
Additional chemotherapy	6 (8)	4 (6)	5 (7)

[†]The Flamingo Wall stent is available in 12 cm with a small diameter or 14 cm with a large diameter

Stent-related recurrent dysphagia was considered present in cases of obstructive tumor growth at the proximal or distal end of the stent, stent migration, food bolus obstruction, or fracture of the stent causing dysphagia during follow-up after stent placement. The most frequently used treatments for stent-related recurrent dysphagia were placement of a second stent, single dose brachytherapy, retrieval or repositioning of migrated stents and endoscopic clearance of stents obstructed by a food bolus. Where a second stent was inserted, this was placed across the area of tumor overgrowth with about 40% of the stent overlapping the lumen of the original stent. For brachytherapy, a guide wire was endoscopicaly inserted into the duodenum. Subsequently, a flexible applicator was passed down the esophagus through which a ^{192}Iridium radio-active source administered a dose of 10-15 Gray at 1 cm from the axis of the applicator.

Endoscopic retrieval of a migrated stent was performed by collapsing the stent through traction on the purse string (lasso) attached to the proximal flange (Ultraflex stent), or by constricting it with a polypectomy snare (Flamingo Wallstent, Z-stent). In some patients with a distally migrated Ultraflex stent or Flamingo Wallstent, it was possible to reposition the stent. This was done by traction with an endoscopic forceps on the upper rim of the Flamingo Wallstent or on the purse string of the Ultraflex stent.

Complete follow-up was obtained for all patients. Patients were evaluated before initial stent placement and at 4-week intervals until death by regular home visits made by a specially trained nurse and/or telephone calls to the patient and the general practitioner. When indicated, patients were readmitted for clinical evaluation, the majority to our hospital but if elsewhere, relevant clinical information was obtained from the admitting hospital.

Statistics

The results were expressed as means ± standard deviation (SD). Dysphagia scores and survival were expressed as medians. Dysphagia was scored as follows: score 0: ability to eat a normal diet; score 1: ability to eat some solid food; score 2: ability to eat some semisolids only; score 3: ability to swallow liquids only; score 4: complete dysphagia (14). Dysphagia scores before and after re-intervention were compared by the Wilcoxon signed-rank test. Survival after re-intervention was analyzed using the Kaplan-Meier method. We compared the incidence of stent-related recurrent dysphagia between the 3 types of stents with the Kaplan Meier method, taking time between initial stent placement and recurrent dysphagia into account. If multiple

incidents of stent-related recurrent dysphagia from the same origin occurred, only the first incident was considered for statistical analysis. Separate multivariate Cox regression analyses were performed to determine predictors of tumor overgrowth, stent migration, and food bolus obstruction. Variables included in the model were age, gender, presence of metastases, histology, length and location of the tumor, type, length and diameter of the stent and dilation before stent placement. We considered a p-value <0.05 as statistically significant.

RESULTS

Seventy-four episodes of stent-related recurrent dysphagia occurred in 63 patients (29%), caused by tumor overgrowth (n=30) (Figure 1A), stent migration (n=26) (Figure 1B), food-bolus obstruction (n=16) (Figure 1C), or fracture of the stent (n=2) (Figure 2). There was no significant difference in the overall incidence of stent-related recurrent dysphagia between the 3 stent types: 28/75 (37%) for the Ultraflex stent, 19/71 (27%) for the Flamingo Wallstent and 16/70 (23%) for the Z-stent (p=0.13) (Table 2). There was a difference in survival after initial stent placement between patients with stent-related recurrent dysphagia compared to patient with no stent-related recurrent dysphagia (median survival with recurrent dysphagia: 189 (95% CI 168-210) days versus with no recurrent dysphagia: 69 (95% CI 49-89) days; p<0.001). Of the patients surviving more than 120 days, 48/98 (49%) developed stent-related recurrent dysphagia.

Tumor overgrowth

The median interval between stent placement and stent-related recurrent dysphagia due to tumor overgrowth was 129 days (Table 3). Tumor overgrowth was observed at the proximal end of the stent (n=15), the distal end (n=13), or at both ends (n=2). Tumor overgrowth occurred less frequently with an Ultraflex stent compared to a Flamingo Wallstent and a Z-stent (p=0.05) (Table 2). None of the other variables included in the model influenced the occurrence of tumor overgrowth.

The predominant strategy for treating tumor overgrowth involved the placement of a second stent. This was performed in 18/30 patients (60%) and in one patient, with tumor overgrowth at both ends of the stents, two stents were placed. Dysphagia scores after placement of a second stent for tumor overgrowth improved from a median of 3 to 1 (n=18; p=0.001). One patient with tumor overgrowth at the proximal end of the stent and treated by a second stent, developed 4 weeks later tumor overgrowth at the distal end, which was treated by a third stent which only

Table 2: Causes of stent-related recurrent dysphagia after placement of an Ultraflex stent (n=75), a Flamingo Wallstent (n=71), or a Z-stent (n=70).

	Ultraflex stent (N=75)	**Flamingo Wallstent (N=71)**	**Z-stent (N=70)**
Total	36 in 28 patients (37%)	22 in 19 patients (27%)	16 in 16 patients (23%)
Tumor overgrowth*	7	12	11
Stent migration*	17	5	4
Food bolus obstruction*	10	5	1
Stent fracture	2		

*p-values adjusted for age, gender, presence of metastases, histology, length and location of the tumor, length and diameter of the stent and dilation before stent placement were respectively: tumor overgrowth: p=0.05, stent migration: p=0.05, food bolus obstruction p=0.06.

Table 3: Outcome of re-intervention after self-expanding metal stent placement for malignant dysphagia in 216 patients.

	Tumor overgrowth (n=30)	**Stent migration (n=26)**	**Food bolus obstruction (n=16)**
Median time after initial stent placement (days)	129 (range 26-364)	92 (range 6-399)	80 (range 8-165)
Effective treatment for recurrent dysphagia	23/25 (92%)	20/24 (83%)	16/16 (100%)
Median dysphagia score before and after reintervention	$3 \rightarrow 2$ (p=0.001)	$3 \rightarrow 1.5$ (p=0.001)	$4 \rightarrow 1$ (p<0.001)
Median survival after re-intervention (days)	55 (range 4-644)	74 (range 11-410)	68 (range 19-616)

*5 patients with tumor overgrowth and 2 patients with stent migration did not receive treatment for recurrent dysphagia

Figure 1: Endoscopic view of tumor overgrowth (A), migration of an Ultraflex stent (B), and food bolus obstruction (C) after placement of a metal stent for palliation of dysphagia due to inoperable esophageal carcinoma.

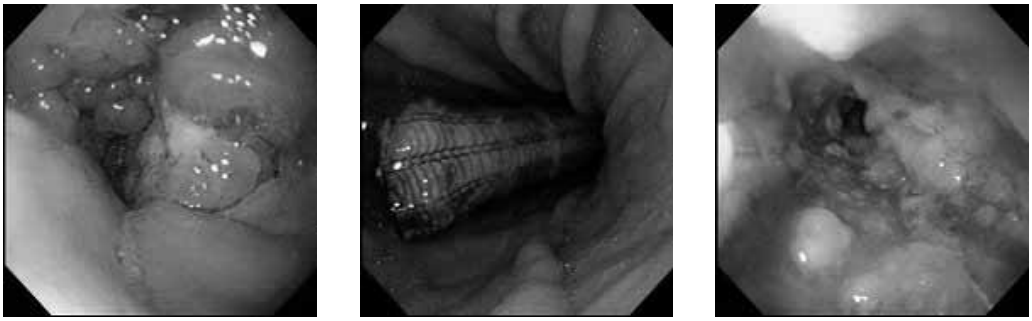


Figure 2: Fractured Ultraflex stent removed from a patient, subsequently followed by placement of a new stent.

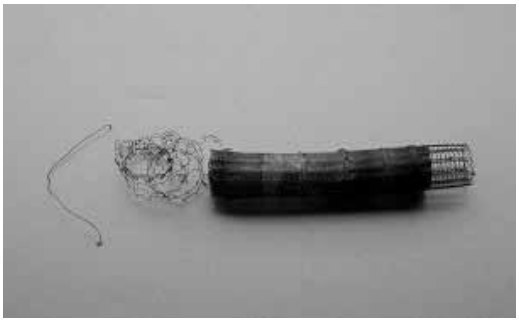
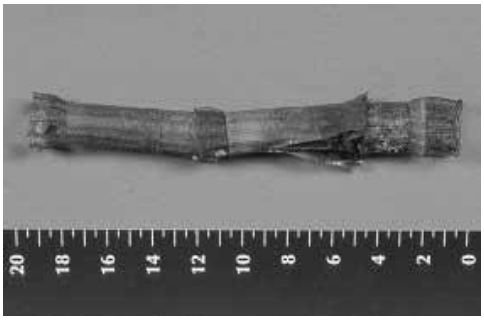


Figure 3: Three stents removed from a patient with inoperable esophageal carcinoma.
This patient first developed recurrent tumor growth at the proximal end of the stent, which was treated by placement of a second stent, followed by tumor overgrowth at the distal end of the first stent, which was treated by placement of a third stent. In an attempt to remove the partially deployed third stent, all three stents were removed.



deployed partially. In an attempt to remove this stent, all three stents were withdrawn (Figure 3) after which the patient was able to eat a fluid diet. Five weeks later a new (fourth) stent was placed. This patient survived for another 5 months after placement of the fourth stent, eventually dying from tumor progression. Another patient had a second episode of recurrent dysphagia due to tumor overgrowth, 182 days after the second stent placement, which was successfully treated by a third stent.

Other treatment modalities for recurrent dysphagia due to tumor overgrowth were dilation (n=1), laser treatment (n=1), external beam radiation therapy (which failed to improve dysphagia) (n=1), and argon plasma coagulation (this patient died 10 days later from tumor progression) (n=1). Two patients received a naso-gastric feeding tube, later replaced by a PEG catheter, and one patient had a subclavian catheter inserted for intravenous feeding. Reasons for the use of other treatment modalities depended on individual patient and tumor characteristics. Five patients received no further treatment, because of progressive disease and a short life expectancy. The median survival after re-intervention for tumor overgrowth was 55 days (Table 3).

Stent migration

The median interval between stent placement and recurrent dysphagia due to stent migration was 92 days (Table 3). Stent migration occurred more frequently with an Ultraflex stent (17/75 (23%)) compared to a Flamingo Wallstent (5/71 (7%)) and a Z-stent (4/70 (6%)) (p=0.05) (Table 2). In particular, long (15 cm) Ultraflex stents were more prone to migrate (10 of the 26 long Ultraflex stents had migrated). There was a trend towards more migrations with the small diameter stents compared to large diameter stents (p=0.07). Location of the stent did not influenced the occurrence of stent migration (mid-esophagus: 4/41 (15%), distal esophagus: 19/122 (16%) and gastric cardia: 3/53 (6%); p>0.20). None of the other variables included in the model influenced the occurrence of stent migration.

Stent migration occurred in 8 (31%) of 26 migrating stents proximally and in 18 (69%) distally, 11 of which into the stomach. Two of these 11 stents were retrieved from the stomach because the patients experienced pain, two stents could be repositioned, and one stent passed the gastrointestinal tract uneventfully. The other 6 stents were left in the stomach without causing symptoms. Proximal stent migration occurred after a median of 46 (range 10-363) days compared to distal migration which occurred after a median of 107 (range 6-399) (p=0.18).

Four patients with stent migration had received chemotherapy (Cisplatinum/Paclitaxel) after placement of the first stent. In total, 15/216 (7%) patients received chemotherapy after stent placement (Table 1). The stents migrated proximally (n=2) or into the stomach (n=2). Both patients with distally migrated stents had a symptomatic complete response following chemotherapy and were able to eat solids again. Nevertheless, due to recurrent tumor growth, a second stent was placed 2.5 and 8 months after migration of the initial stent. Both patients with proximally migrated stents complained of dysphagia, necessitating the placement of a second stent.

For stent migration the predominant strategy was placement of a second stent in 14/26 patients (54%), which was effective in 13/14 patients (93%). One patient returned with recurrent dysphagia one week after placement of a second stent. Endoscopy showed that this stent had migrated as well. A third stent was inserted, however, dysphagia persisted for unknown reasons, and a naso-gastric feeding tube was placed. Another strategy was repositioning of the stent, performed in another 7 of these 26 patients (27%). Repositioning was effective in 5/7 patients (71%). All these stents had migrated distally (2 of which into the stomach). In 2/7, the repositioning procedure failed because the stent migrated again. After stent migration, two patients received brachytherapy (which failed to improve the dysphagia score in one patient), one patient received a naso-gastric feeding tube and two patients remained free of dysphagia in spite of stent migration, both having undergone chemotherapy with a complete clinical response after stent placement (see above).

The median dysphagia scores after re-intervention for stent migration improved from 3 to 1.5 (n=26; p=0.001), and median survival after re-intervention was 74 days (Table 3).

Food-bolus obstruction

The median interval between stent placement and recurrent dysphagia due to food bolus obstruction was 80 days (Table 3). There was a trend that food bolus obstruction occurred more frequently with an Ultraflex stent than with a Flamingo Wallstent and a Z-stent (p=0.06; Table 2). None of the other variables included in the model influenced the occurrence of food bolus obstruction.

In all cases, the strategy was endoscopic stent clearance. Four patients had repeated episodes of food bolus obstruction. In one patient this was caused by a small fracture in the cover of the stent. One other patient experienced fracture of the metal mesh of an Ultraflex stent (Figure 2). Both these stents were removed and new stents

were successfully placed. The median dysphagia score after re-intervention for food bolus obstruction improved from a median of 4 to 1 (n=16, $p<0.001$), and the median survival after re-intervention was 68 days (Table 3).

DISCUSSION

Stent-related recurrent dysphagia after metal stent placement for non-resectable carcinomas of the esophagus or the esophagogastric junction occurred in almost one third of our patients. This was mainly caused by tumor overgrowth at the proximal and/or distal end of the stent, stent migration, and food bolus obstruction. The incidence of stent-related recurrent dysphagia in our study population was in accordance with findings in other series, where an incidence of stent-related recurrent dysphagia has been reported varying between 22% and 50% (4-7, 10). Re-intervention for stent-related recurrent dysphagia was effective in over 90% of our patients and improved dysphagia in most of these patients. Survival after re-intervention was longer than 2 months.

In the majority of patients with tumor overgrowth (60%), the successful treatment strategy was placement of a second stent. Incidentally other treatments were used with variable results. Tumor overgrowth affected both ends of the stent at a similar rate. As tumor overgrowth occurred after a median of 129 days (range 26-364), it was likely to have been the result of tumor growth rather than an incorrect stent positioning. Tumor overgrowth was histologically confirmed in the majority of patients. We did not observe recurrent dysphagia due to nonmalignant obstructive tissue, such as granulation tissue, reactive hyperplasia and fibrosis at the proximal or distal end of the stent. Mayoral et al. (15) reported this cause of recurrent dysphagia in more than 30% of their patients at a mean interval of 22 weeks after stent placement. We observed the development of this nonmalignant tissue in a number of patients undergoing endoscopy for reasons other than recurrent dysphagia. It was predominantly found at the proximal end of the stent but did not cause dysphagia. In theory, tumor overgrowth could be delayed by using stents which, after expansion, are approximately 2-4 cm longer than the stricture to allow for a 1-2 cm tumor growth above the proximal and below the distal end of the stent. In our opinion, prevention of tumor overgrowth should be an important issue in the design of new stent types. Possibly this could be achieved by impregnating metal stents with chemotherapeutic agents or the incorporation of beta-radiation emitting agents (16, 17). Further randomized trials would be needed to establish whether such modifications could, in practice, result in longer stent patency without

increasing stent-related complications, such as fistula formation or stricture formation at either end of these modified stents.

Stent migration, which occurred in 12% of our patients, involved distal migration in over two-thirds, eleven stents (5.5%) ending up in the stomach. In two patients, this led to upper abdominal pain, particularly after eating and/or drinking, necessitating retrieval of these two stents. Since endoscopy revealed no clear explanation, we hypothesized that the pain was caused by an irritating effect of the stent on the gastric wall. We endorse the recommendation made by others that stent retrieval from the stomach is probably only indicated in a minority of patients in whom a migrated stent causes pain or obstruction of the pylorus, or if it hampers successful placement of a second stent. Perforation or obstruction of the digestive tract are uncommon complications of stent migration (11, 18).

Our predominant strategy in stent migration was placing a second stent (14/26), which was effective in 13/14. A more cost-effective strategy to stent migration might be the repositioning of the migrated stent. Thanks to their mechanical properties, the Ultraflex stent and the Flamingo Wallstent were easier to reposition or remove endoscopically than the Z-stent. This is done by traction at the upper rim of the Flamingo Wallstent or at the purse string (lasso) attached to the inside of the proximal flange of the Ultraflex stent, a procedure which was successful in 5 of 7 patients. Others have described a different technique of repositioning a stent by placing the endoscope in a retroflexed position and using it a as a 'hook'. This method can be applied successfully with the Ultraflex stent (19)], however it cannot be used for the Z-stents, because it can result in a 'kink' in the stent, damaging the esophageal mucosa and preventing it from being removed (20).

Four patients in whom the stent migrated had received chemotherapy after stent placement. The effect of chemotherapy on the tumor itself was likely the cause of stent migration, particularly in the two patients with distally migrated stents, as these patients had a complete (temporary) response on chemotherapy treatment. Presently, whenever a patient is scheduled to undergo treatment with chemotherapy, we only place a stent if the patient has received at least 2 courses of chemotherapy and is still complaining of persistent dysphagia with evidence of stable or progressive malignant disease at endoscopy. If a patient is not able to drink enteral feeding in the initial period, we prefer to place a naso-gastric tube for feeding. In the future, these group of patients may be candidates for the placement of a bio-absorbable stent. These stents have the advantage that disintegration of the stent occurs over time, and therefore stent retrieval is probably no longer necessary (21).

Stent design may play a role in stent migration. In our study, stent migration occurred frequently with Ultraflex stents. This can, at least partly, be explained by the lower expansion force of the Ultraflex stent compared to the other two stent types (22). In addition, migration of the Flamingo Wallstent is prevented by the proximal increase in diameter inherent to the conical shape. Moreover, the change in the braiding angle between the proximal and distal parts of the Flamingo Wallstent mesh allows the distal part of this stent to stretch in response to peristaltic traction. The European Z-stent has metal barbs on the outside of the stent to anchor it into the tumor (22, 23). There was a trend towards fewer stent migrations after placement of a large diameter stent. We previously reported however, that in a non-randomized study comparing 19 large diameter Flamingo Wallstents with 21 small diameter Flamingo Wallstents five of seven complications (mainly perforation and bleeding) occurred with large diameter stents ($p=0.07$) (23). Therefore, widespread use of larger diameter stents should wait until comparative studies have proven their greater efficacy without compromising safety. Since stent migration has been reported to occur less frequently with uncovered stent types , new stent types, particularly a design with a double layer consisting of a covered inner layer and an uncovered outer layer, are currently under investigation.

For food bolus obstruction, the successful strategy was endoscopic stent clearance. As a stent lumen has a fixed diameter and lack peristalsis, food bolus obstruction is usually caused by a discrepancy between the size of the bolus and the lumen of the stent. Smaller food particles of a fibrous nature may sometimes adhere together to form an obstruction and food particles can also be snagged on defects in the stent cover as occurred in one of our patients. Therefore, it is important not to damage the stent cover during placement or re-intervention and in cases of recurrent obstruction. Careful endoscopic inspection can detect such defects, which necessitate the replacement of the damaged stent.

Prevention consists of providing clear eating instructions, specifically, very thorough chewing of food, especially meat, and drinking effervescent drinks between bites and after meals in order to flush the stent. Although our patients received instructions in a brochure, food bolus obstruction still occurred in 16/216 (7%) patients.

In conclusion, although self-expanding metal stent placement is a safe and effective treatment for malignant dysphagia, stent-related recurrent dysphagia occurred in almost one-third of our patients. Re-intervention for stent-related recurrent dysphagia was generally effective and improved dysphagia scores. The most effective treatment strategy for both tumor overgrowth and stent migration was

placement of a second stent, or, in cases of migration, stent repositioning. Innovations in stent design could potentially reduce the risk of these two causes of stent-related recurrent dysphagia and thereby increase the effectiveness of metal stents. For food bolus obstruction, endoscopic stent clearance was a universally effective treatment strategy. Our findings confirm the importance of referring patients with recurrent dysphagia after stent placement for endoscopic investigation as this problem is almost always amenable to treatment.

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6

Brachytherapy
versus
Stent placement

6A

Single dose brachytherapy versus metal stent placement for the palliation of dysphagia from esophageal cancer

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ABSTRACT

Background: Both single dose brachytherapy and self-expanding metal stent placement are commonly used for the palliation of esophageal obstruction due to inoperable cancer, but their relative merits are unknown.

Methods: Between December 1999 and June 2002, 209 patients with dysphagia from inoperable carcinoma of the esophagus or gastro-esophageal junction were randomized to placement of an Ultraflex stent (n=108) or single dose (12 Gy) brachytherapy (n=101). Patients were followed by monthly home visits from a specialized nurse who collected outcome data using standardized questionnaires on relief of dysphagia, health-related quality of life, and costs. In addition, complications and treatments for persistent or recurrent dysphagia were recorded.

Results: Dysphagia improved more rapidly after stent placement than after brachytherapy, but long term relief of dysphagia was better after brachytherapy. Complications occurred more often after stent placement (stent: 36/108 (33%) vs. brachytherapy: 21/101 (21%); p=0.02), which was mainly due to a higher incidence of late hemorrhage (14/108 (13%) vs. 5/101 (5%); p=0.05). The number of patients treated for persistent or recurrent dysphagia was similar for both treatment groups (stent: 43/108 (40%) vs. brachytherapy: 43/101 (43%)), as was median survival (stent: 145 (95% CI: 103-187) vs. brachytherapy: 155 (95% CI: 127-183) days). There was a benefit in general and disease-specific quality of life scores in favor of brachytherapy compared to stent placement. Total medical costs, including hospital stay, re-treatment and extramural health care, were similar at € 8,215 for stent placement and € 8,135 for brachytherapy.

Conclusions: Despite a less rapid improvement, single dose brachytherapy gave a better long term relief of dysphagia. Since brachytherapy was also associated with fewer complications than stent placement, it is recommended as the initial treatment for the palliation of dysphagia from esophageal cancer.

INTRODUCTION

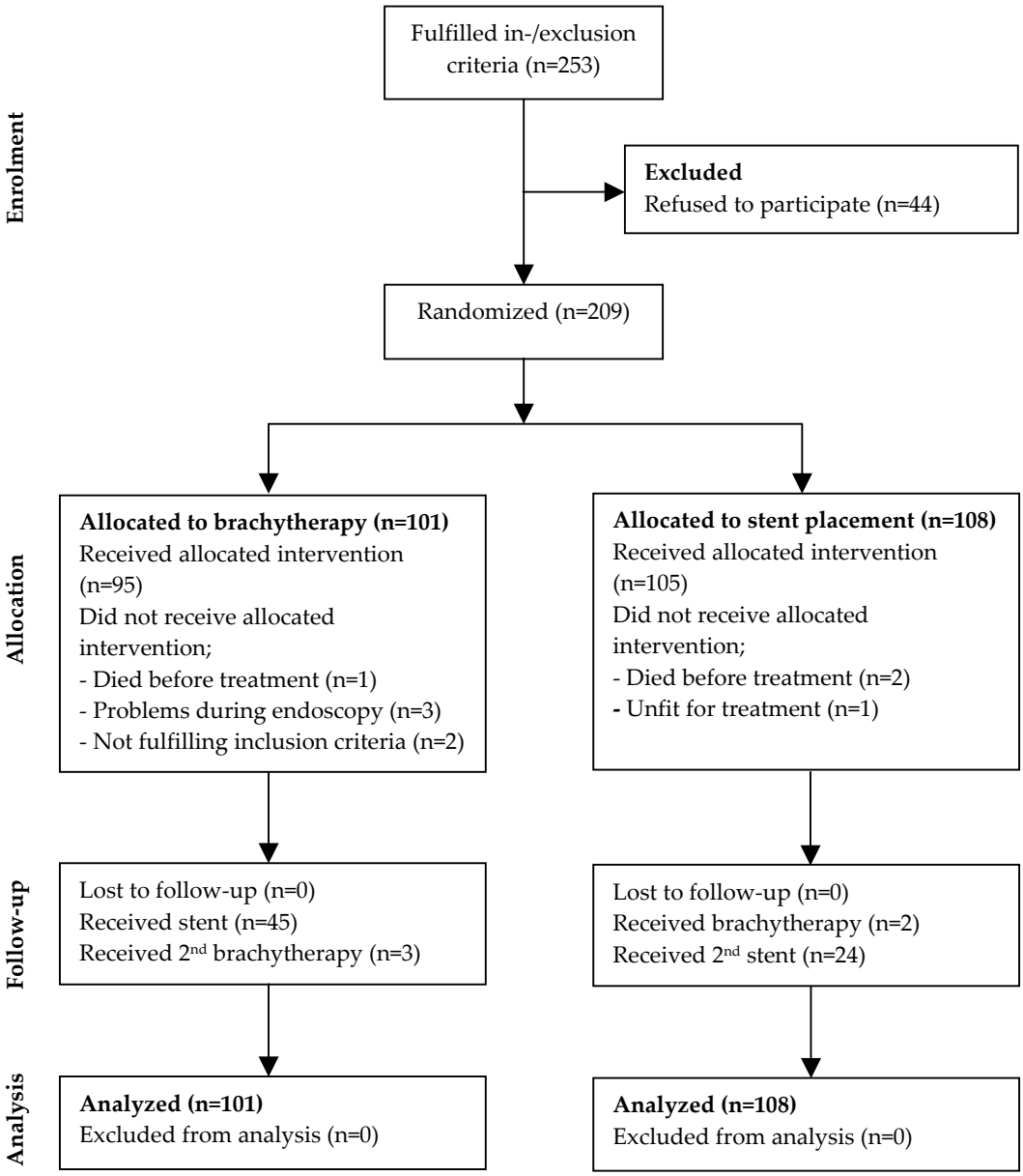
Annually, approximately 400,000 patients are diagnosed with esophageal cancer world-wide, and more than 350,000 die of this malignancy, which makes esophageal cancer the eighth most common cancer, and sixth on the list of cancer mortality causes (1). The incidence of esophageal carcinoma has risen markedly over the past two decades in the Western world, due to a marked increase in the incidence of adenocarcinoma (2, 3). The prognosis of esophageal cancer is poor with a 5-year survival of 10-15% (4, 5). Moreover, more than 50% of patients with esophageal cancer have already inoperable disease at presentation. The majority of these patients require palliative treatment to relieve progressive dysphagia or fistula formation. Presently, endoscopic placement of a covered self-expanding metal stent is the treatment of choice for an esophago-respiratory fistula. Treatment options most commonly used for palliation of dysphagia include self-expanding metal stent placement (6-10), laser therapy (11, 12), external beam radiation in combination with brachytherapy (13, 14), and brachytherapy as a single treatment (15-18). A disadvantage of laser therapy is that repeated treatment sessions are required to achieve and maintain adequate palliation (11, 12). A combined treatment of external beam radiation with brachytherapy is often too intensive for patients with inoperable, metastatic disease and a poor medical condition. Therefore, in many patients with inoperable disease, placement of a self-expanding metal stent or single dose brachytherapy are used for the palliation of dysphagia (19). Both these treatment modalities have been proven to be effective in relieving dysphagia with a low complication rate (7-10, 15-18), however, their relative effectiveness is unknown. In the present study, patients presenting with inoperable cancer of the esophagus or gastro-esophageal junction were randomized to stent placement or single dose brachytherapy. We compared the two treatments with respect to relief of dysphagia, complications, treatment for persistent or recurrent dysphagia, health-related quality of life, and costs (20).

METHODS

Study population

Between December 1999 and July 2002, 253 consecutive patients with progressive symptoms from esophageal obstruction due to inoperable cancer were eligible to enter the trial. Since 44 patients refused to participate, 209 patients were randomized to self-expanding metal stent placement or single dose brachytherapy (Figure 1).

Figure 1: Flow chart of the study comparing brachytherapy with stent placement for inoperable carcinoma of the esophagus or gastro-esophageal junction.



Inclusion criteria included inoperable cancer of the esophagus or gastro-esophageal junction due to metastatic disease (as defined by the TNM-classification) and/or a poor medical condition (unfit to undergo surgery) with a dysphagia score of 2-4 on the dysphagia score scale (21), and a written informed consent. Exclusion criteria were a tumor length of more than 12 cm, tumor growth within 3 cm of the upper esophageal sphincter, deep ulceration or a trachea-esophageal fistula, macroscopic or microscopic tumor growth into the tracheal lumen, the presence of a pacemaker, and previous radiation therapy or stent placement.
The study was approved by the Central Committee on Research Involving Human Subjects in The Netherlands. Participating centers included 3 university and 6 general hospitals as listed in the Appendix.
For randomization, patients were stratified for location of the tumor (esophagus or gastro-esophageal junction) and for administration of chemotherapy prior to treatment. Randomization was centrally performed by telephone at the Trial Office of the Department of Oncology, Erasmus MC Rotterdam.

Interventions

Prior to both interventions, an endoscopy was performed. Dilation was performed on indication to a maximum of 11 mm by a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC, USA). The proximal and distal tumor margins were marked by injecting radiographic contrast medium into the submucosa of the esophageal wall through a sclerotherapy needle. Then a guide wire was left.
For patients randomized to stent placement, the partially covered Ultraflex stent (Boston Scientific, Natick, MA, USA) was used, which is available in lengths of 10, 12 and 15 cm with a proximal diameter of 23 mm and a distal diameter of 18 mm. The stent was introduced and deployed under fluoroscopic monitoring. The stent length was at least 3 cm longer than the stricture to allow for at least a 1.5 cm extension above and below the proximal and distal tumor margins. Following placement, deployment of the stent was assessed endoscopically and radiographically.
For brachytherapy, a flexible applicator (Bonvoisin-Gérard Esophageal Applicator, Nucletron, Veenendaal, The Netherlands) with a diameter of 10 mm was passed down the esophagus. A single dose of 12 Gy was administered with the radioactive source ^{192}Iridium at 1 cm from the source axis of the applicator. The standard active length of the application was the tumor length plus two centimeters extra at both ends of the tumor.

All patients were consciously sedated with midazolam during either treatment procedure. Sucralfate was prescribed for a period of 4 weeks after brachytherapy as a prophylactic measure for odynophagia. A lifelong daily dose of 40 mg omeprazole was prescribed to all patients of whom the distal end of the stent or the active length of application of brachytherapy was below the gastro-esophageal junction to prevent gastro-esophageal reflux after the procedure.

Study endpoints

The primary outcome of the study was dysphagia score (21) during follow-up; secondary outcomes included complications, treatment for persistent or recurrent dysphagia, health-related quality of life, and costs.

Dysphagia was scored as follows: score 0: ability to eat a normal diet; score 1: ability to eat some solid food; score 2: ability to eat some semisolids only; score 3: ability to swallow liquids only; score 4: complete obstruction (21). Major complications were defined as life-threatening or severe complications, such as perforation, hemorrhage (hematemesis, melena, or a significant drop in hemoglobin level), fever, fistula formation and severe pain, whereas minor complications were defined as not life-threatening or moderately severe complications, such as mild pain and gastro-esophageal reflux. Early complications were defined as complications occurring within seven days after treatment. Complications occurring more than seven days after treatment were defined as late complications, although it was often not known whether these were related to the treatment or to progression of the disease. Persistent dysphagia was defined as continuing dysphagia 2-4 weeks after treatment with tumor growth observed at endoscopy, necessitating a second treatment. Recurrent dysphagia was defined as occurrence of tumor regrowth more than four weeks after treatment, stent migration, food bolus obstruction or fracture of the stent causing dysphagia. If more incidents of recurrent dysphagia of the same origin occurred, only the first incident was considered for analysis. The choice of the treatment modality for complications, and persistent or recurrent dysphagia was made by the responsible physician.

Health-related quality of life was assessed using the oncology-specific European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 measure (22), the esophageal cancer specific EORTC OES-23 measure (23), the EuroQol-5D measure (24) including a self-classifier with 5 questions and a visual analogue scale (EQ-VAS) for the measurement of overall self-rated health, and a visual analogue pain scale. Total medical costs included initial costs of treatment, hospital stay, re-treatment costs, medical services, and extramural health care (25). We estimated full

cost prices on the basis of real resource use from a societal perspective. Volumes of care were recorded for all patients and unit prices were determined with a microcosting method (25). All costs are reported in Euros for the year 2002.

Follow-up

Patients were prospectively followed by home visits of one of six specially trained research nurses at 14 days, 1 month and then monthly until one year after treatment. After one year of follow-up, patients were visited every 3 months, and/or telephone calls to the patient and the patients' practitioner were made. Patients received a diary in which they scored dysphagia daily until 1 month and thereafter weekly. Questionnaires for assessing quality of life were filled out on the day of treatment and during each home visit. Diary and questionnaires were completed, if necessary, by the research nurse. The response was more than 90% during the entire follow-up period (in total 681/724 (94%) questionnaires were collected in the brachytherapy group and 717/752 (95%) in the stent group). The use of medical services and extramural health care was assessed during home visits by a standardized checklist. If indicated, patients were readmitted for clinical evaluation. All participating clinicians filled out standardized case record forms during control visits, re-treatments and admissions.

Statistics

Analyses were performed on an intention-to-treat basis with follow-up data until February 2003. The improvement in dysphagia score by at least one grade at 30 days after treatment was compared between treatment groups with a X^2-test. This comparison was calculated to have a 90% power with a sample size of 104 patients in each group (α=0·05) if the improvement in dysphagia was 89% after stent placement and 70% after brachytherapy (15, 16, 26, 27). The dysphagia score at different time points between treatment groups was compared with a linear regression model that included the baseline dysphagia score to adjust for any pre-treatment differences between the groups. Time was included as a restricted cubic spline function, which was chosen because of its flexibility and smoothness (28). The interaction between time and treatment group was also included to allow for the presence of different time courses in the two groups. Survival of the two groups was calculated and compared using Kaplan-Meier curves and the log rank test. Survival was combined with dysphagia score to calculate dysphagia-adjusted survival. The area under the curve represented the number of days alive without or with mild

dysphagia (dysphagia score 0 or 1). We tested the difference between areas with a non-parametric bootstrap procedure. We drew 2000 samples with replacement and determined the empirical 95% confidence interval and p-value (29). Complications and treatment for persistent or recurrent dysphagia between the two groups were compared using Kaplan-Meier and log rank tests to adjust for time of occurrence of the event and survival differences. We analysed quality of life scores with analysis of repeated measurements (30). For each scale a model was fitted that included day and treatment group as fixed factors, and the baseline measure and interaction between day and treatment group as covariates. A simple compound symmetric covariance structure was assumed to hold for all scales. For easier interpretation of differences between randomised groups, we also estimated the average differences over time for scales where no clear interaction was noted ($p>0.10$). Since cost data per patient are typically highly skewed, we used non-parametric bootstrap techniques to derive a p-value for the differences in distribution of the direct medical costs (31). We considered a p-value $<0{\cdot}05$ statistically significant. Calculations were performed with SPSS 9·0 (SPSS Inc., Chicago, IL, USA), SAS 8·2 (SAS Institute Inc., Cary, NC, USA), and S-plus 2000 (Insightful Inc., Seattle, WA, USA).

RESULTS

Patient demographics

The two patient groups were comparable with respect to clinical characteristics (Table 1). Three patients died before treatment due to progression of the disease, one patient was considered to be unfit to undergo metal stent placement at the day of treatment, and five patients did not receive the allocated intervention (Figure 1).

Functional outcome and survival

The dysphagia score improved more rapidly after stent placement than after brachytherapy (Figure 2). At 30 days after treatment, however, dysphagia score improvement was not significantly different between stent placement and brachytherapy any longer. At this time, dysphagia score had improved by at least one grade in 64/88 (73%) patients after brachytherapy and in 70/92 (76%) patients after stent placement ($p=0.61$). In the long term, the dysphagia score was better after brachytherapy than after stent placement, although the difference became smaller with overlapping confidence intervals after about 350 days (Figure 2).

Table 1: Clinical characteristics of 209 patients randomized to brachytherapy or stent placement for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction.

	Brachytherapy N=101	**Stent placement N=108**
Age (years (SD))	69 (13)	69 (11)
Gender (M/F)	76/25	86/22
Dysphagia score before treatment (mean (SD))	2.8 (0.9)	2.8 (0.7)
Tumor length (cm) (mean (SD))	7.5 (2.6)	7.5 (2.8)
Indications for palliative therapy		
Metastases	66 (65%)	68 (63%)
Poor medical condition	23 (23%)	28 (26%)
Both	12 (12%)	12 (11%)
Location of tumor		
Esophagus	86 (85%)	93 (86%)
Gastro-esophageal junction	15 (15%)	15 (14%)
Tumor histology		
Squamous cell carcinoma	29 (29%)	29 (27%)
Adenocarcinoma	69 (68%)	75 (69%)
Other	3 (3%)	4 (4%)
Prior chemotherapy	13 (13%)	17 (16%)

Taking survival into account, patients randomized to brachytherapy had more days with almost no dysphagia (grade 0 or 1) during follow-up than patients randomized to stent placement (115 days versus 82 days, difference 33 days, 95% CI 1-64 days, p=0.015) (Figure 3). Median survival was 155 (95% CI: 127-183) days after brachytherapy and 145 (95% CI: 103-187) days after stent placement (p=0.23) (Figure 3).

By February 2003, 158 patients had died from tumor progression, 7 patients from hemorrhage, of which it was unclear whether this was due to tumor progression, to the treatment or another unrelated cause, and 3 patients had died from the complications of perforation. Twenty-five patients had died from a cause unrelated to the tumor or treatment, and the remaining 16 patients were still alive with a follow-up of at least 6 months (range 6.4-31.8 months).

Figure 2: Dysphagia scores (scored on a scale from 0 (normal) to 4 (complete dysphagia)) in patients randomized to brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction. The symbols Δ and O represent mean dysphagia scores, the lines are spline functions with 95% confidence intervals.

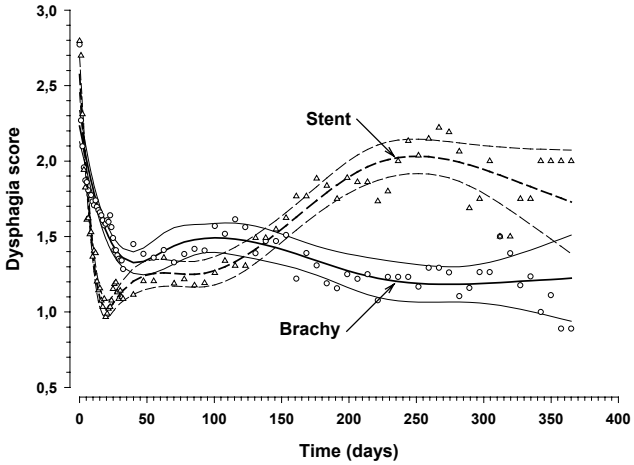


Figure 3: (Dysphagia-adjusted) survival after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction. The upper 2 survival curves represent the percentage of all patients alive after brachytherapy or stent placement. The lower 2 dysphagia-adjusted survival curves represent the percentage of patients alive without or with mild dysphagia (dysphagia score 0 or 1).

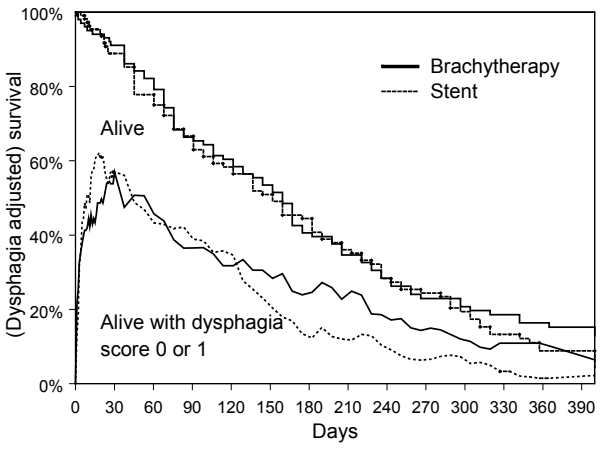


Table 2: Complications and persistent/recurrent dysphagia in 209 patients randomized to brachytherapy or stent placement for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction.

	Brachytherapy N=101	**Stent placement N=108**	p-value*
Total complications	23 in 21 patients (21%)	45 in 36 patients (33%)	p=0.02
Major complications	14 in 13 patients (13%)	28 in 27 patients (25%)	p=0.02
≤ 7 days			
Perforation	1	2	
Fever	1	1	
Severe pain		2	
(Aspiration) pneumonia	1	1	
> 7 days			
Perforation	1		
Fever	1		
Hemorrhage	5	14	
Fistula formation	3	3	
Severe pain	1	1	
Pressure necrosis		3	
Pre-stenotic dilation		1	
Minor complications	8 in 8 patients (8%)	16 in 16 patients (15%)	p=0.08
Mild retrosternal pain	5	9	
Gastro-esophageal reflux	1	5	
Radiation esophagitis	1		
Candida infestation	1	2	
Persistent/recurrent dysphagia	53 in 43 patients (43%)	52 in 43 patients (40%)	p=0.81
Tumor persistence	18	0	
Tumor regrowth	26	16	
Stent migration	3[#]	18	
Food bolus obstruction	5	16	
Fracture of stent		2	
Oblique position stent	1[#]		

* Log rank test for time to first complication

[#] Some patients randomized to brachytherapy later received a stent for various reasons.

Complications and treatment for persistent and recurrent dysphagia

Complications occurred more frequently after stent placement than after brachytherapy (p=0.02) (Table 2). Major complications included 4 perforations, 2 in each treatment group, resulting in the death of three patients. Late major complications consisted predominantly of hemorrhage (n=19) at a median of 123 days (range 12-280) after treatment. Hemorrhage occurred more frequently after stent placement (n=14) than after brachytherapy (n=5) (p=0.05). Thirteen (9 in the stent group) of these patients underwent an endoscopy. In 8 patients (6 in the stent group), the hemorrhage was clearly caused by bleeding from the tumor, whereas in the other 5 patients the cause was unclear. In 7 patients, one or more blood transfusions were given, and 6 patients were treated with external beam radiation. Seven patients died from this complication (1 patient randomized to brachytherapy and 6 to stent placement). Fistula formation (n=6) occurred at a similar rate in both groups after a median of 209 (range 13-448) days.

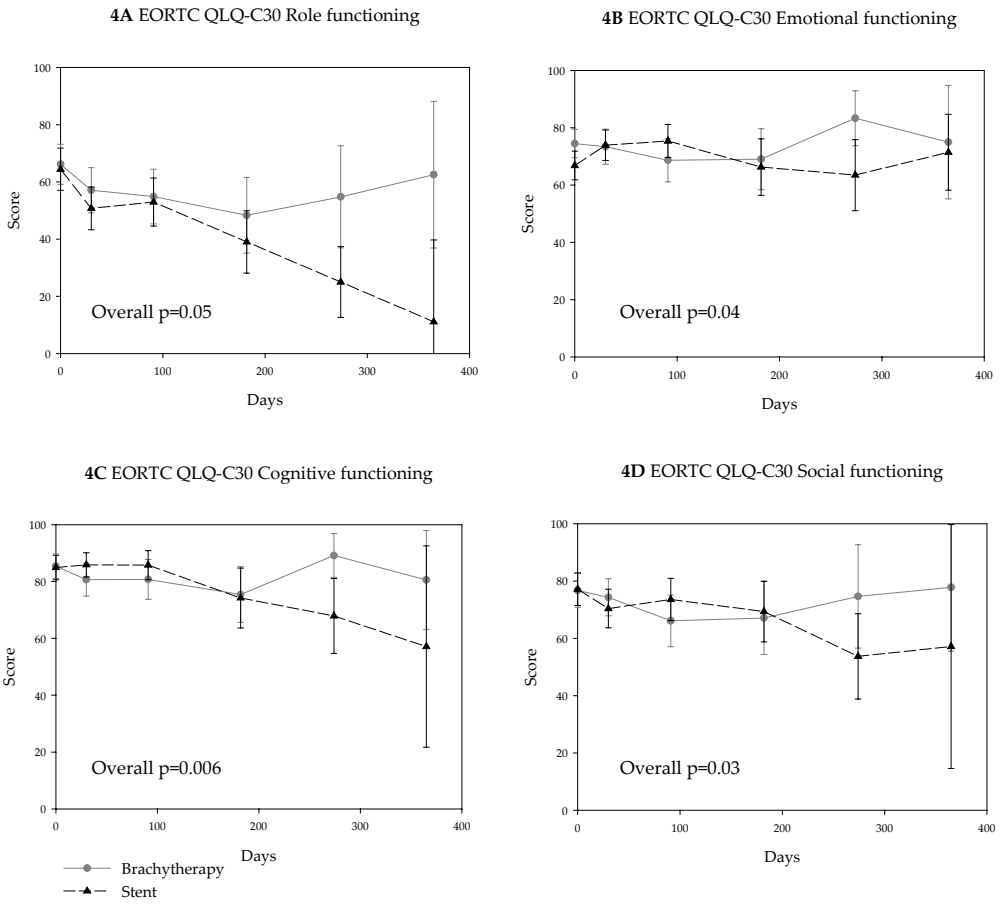
There was a trend towards more minor complications, in particular mild retrosternal pain and gastro-esophageal reflux, after stent placement (p=0.08) (Table 2). Retrosternal pain was effectively treated with analgesics, gastro-esophageal reflux with omeprazole.

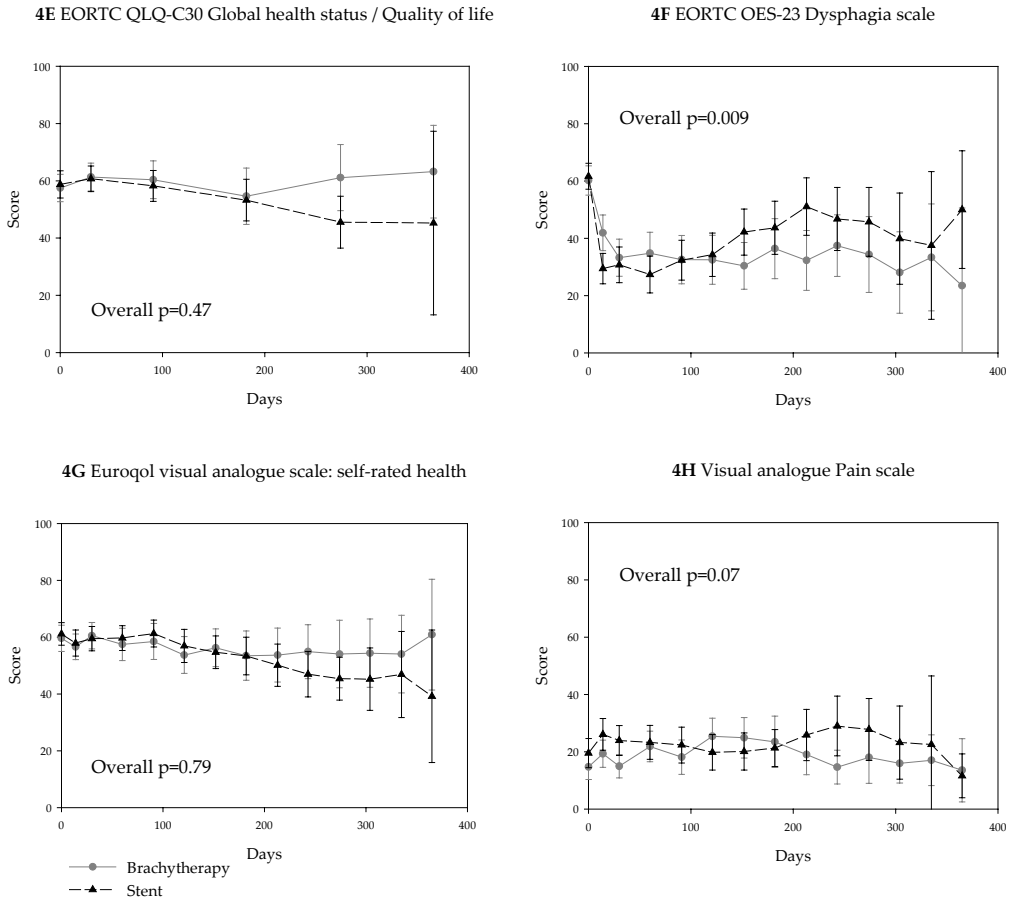
The number of patients treated for persistent or recurrent dysphagia was not different between the two treatment groups (Table 2). Eighteen of 101 (18%) patients randomized to brachytherapy had persistent dysphagia 2-4 weeks after treatment. Endoscopy confirmed persistent tumor growth and a stent was placed. Tumor regrowth occurred in 26 patients after brachytherapy, which was treated by placement of a stent (19/26; 73%), a second dose of brachytherapy (3/26; 12%), or another treatment (4/26; 15%). Recurrent dysphagia after stent placement was predominantly caused by tumor overgrowth, stent migration or food bolus obstruction (Table 2). Tumor overgrowth was treated by placement of a second stent (11/16; 69%), or a variety of other treatments; stent migration by placement of a second stent (9/18; 50%), repositioning of the stent (7/18; 39%), or another treatment; food obstruction by endoscopic cleaning of the stent.

Health related quality of life

There was a benefit over time for brachytherapy on the majority of the health related quality of life scales (Figure 4A-H). For the oncology specific EORTC QLQ-C30 measure, there were overall differences between brachytherapy and stent placement on several functional scales including role functioning (p=0.05), emotional

Figure 4: Quality of life scores after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction, including the role functioning (4A), emotional functioning (4B), cognitive functioning (4C), social functioning (4D), and global health status (4E) scales from the EORTC QLQ-C30 measure, the dysphagia scale from the EORTC OES-23 measure (4F), the EuroQol visual analogue scale for self-rated health status (4G), and the visual analogue pain scale (4H). Graphs show the mean scores with 95% confidence intervals of the different quality of life scales during follow-up. Higher scores represent a better functioning or quality of life, except for the dysphagia scale (4F) and pain scale (4H) were higher scores represent more dysphagia or pain.





functioning (p=0.04), cognitive functioning (p=0.006) and social functioning (p=0.03) (Figure 4A-D). The differences between treatments on these scales were small at the beginning of follow-up and more pronounced at later time points. For emotional, cognitive, and social functioning (Figure 4B-D), the differences in effect over time were statistically significant (interactions between time and treatment group $p<0.05$). The average difference over time was 6.5 points in favour brachytherapy for role functioning (Figure 4A), and 2.7 points for global health status (Figure 4E). For the disease specific EORTC OES-23 measure, there was an overall significant difference on the dysphagia scale (p=0.009, Figure 4F). The interaction between time and treatment group was significant which is in agreement with the observation that stent placement was better at the beginning of follow-up and became worse at later time points. There was no significant difference on the EuroQol visual analogue

scale for overall self-rated health (Figure 4G, average difference 1.5 points). There was a trend towards less pain in the brachytherapy group (average difference 3.8, Figure 4H).

Medical costs

The initial costs of stent placement (€ 1,500) were higher than the costs of brachytherapy (€ 570). The total medical costs were however similar (stent € 8,215 vs. brachytherapy € 8,135, p=0·87, Table 3). Hospital re-admission during follow-up occurred frequently in both groups. Total hospital stay during follow-up was 11·5 days after stent placement versus 12·4 days after brachytherapy, causing high intramural costs (€ 5,675 vs. € 6,085, p=0·85). Costs for the use of medical procedures during follow-up were higher after stent placement (€ 250 vs. € 170, p=0·01).

Table 3: Average medical costs (in €) per patient of brachytherapy or stent placement for dysphagia due to inoperable carcinoma of the esophagus and gastro-esophageal junction.

Cost category	Brachytherapy N=101	Stent placement N=108	p-value[5]
Total treatment[1]	1415	1945	p=0.001
Total intramural care[2]	6085	5675	p=0.85
Medical procedures[3]	170	250	p=0.01
Extramural care[4]	465	345	p=0.81
Total	**8135**	**8215**	**p=0.87**

[1]Costs include initial treatment costs and additional placement of a stent after brachytherapy or placement of a second stent.
[2]Costs include hospital stay and visits to outpatient clinic.
[3]Costs include medical procedures related to the treatment, for example endoscopy, X-ray.
[4]Costs include for example visits to the general practitioner and tube feeding.
[5]Derived from 2000 bootstrap samples drawn with replacement

DISCUSSION

This is the first randomized study that compares the two most widely used methods for the palliation of dysphagia due to inoperable cancer of the esophagus or gastro-esophageal junction, i.e. single dose brachytherapy and stent placement. Brachytherapy resulted in a better relief of dysphagia at longer follow-up and was associated with fewer complications. In addition, there was a slight benefit in

quality of life after brachytherapy. The number of repeated procedures for persistent or recurrent dysphagia and costs of both treatment modalities were similar.

In this study, we obtained detailed longitudinal data on the course of dysphagia. In this way, we were able to investigate the expected delay in treatment effect after brachytherapy during the first few weeks (Figure 2). In the long term, dysphagia scores were better in the group of patients randomized to brachytherapy. The long-term benefit in the brachytherapy group could not be ascribed to the fact that patients who had persistent dysphagia after brachytherapy were treated with a stent (n=18). This group had worse dysphagia scores than the stent group or the brachytherapy group without persistent dysphagia until 3 months of follow-up. After 3 months, the dysphagia scores were not different from the dysphagia scores in the stent group (results not shown). This confirms that brachytherapy as the initial treatment was more effective in the relief of dysphagia at longer follow-up.

Complications occurred more often after stent placement than after brachytherapy. A common late complication was the occurrence of hemorrhage, in particular in patients treated with a stent. It is possible that in some patients, especially in those who died, this was caused by the stent exerting pressure on the tumor and/or the normal mucosa of the esophagus. A few case reports have been published on massive hemorrhage after stent placement caused by perforation of the stent through the esophageal wall into the aorta (32, 33). In the literature, reported incidence rates of hemorrhage after brachytherapy vary between 0% and 5% (15, 16, 18, 26). In contrast, incidences varying between 5% and 16% have been reported after stent placement (7-10). Whether the radiation effect of brachytherapy has a protective effect on bleeding from the tumor through tumor reduction or injury to the tumor vasculature (34), or that the expanding force of a stent increases this risk remains to be elucidated.

Many patients in both treatment groups needed treatment for persistent or recurrent dysphagia (Table 2). After brachytherapy, a second treatment was most commonly the placement of a stent, because of persistent or recurrent tumor growth. It can be debated whether a single treatment of 12 Gy brachytherapy was the optimal dose, or that the biological effects of brachytherapy might be improved by increasing and/or fractionating the delivered dose. Different doses of brachytherapy were compared previously in 172 patients with advanced esophageal (mainly squamous cell) carcinoma (27). Patients were randomized to receive 12 Gy in 2 sessions, 16 Gy in 2 sessions or 18 Gy in 3 sessions. Patients who received 16 or 18 Gy did significantly better than patients who received 12 Gy in 2 sessions in terms of dysphagia-free survival and persistent tumor growth in the oesophagus after treatment. The

treatment regimes with 16 Gy in 2 sessions and 18 Gy in 3 sessions were again compared in a randomized trial with 232 patients, with similar results for the two treatment regimes (18). Therefore, additional studies are needed to investigate whether a higher and/or fractionated dose of brachytherapy will increase the efficacy of dysphagia relief in patients with metastatic disease and/or a poor general condition.

The need for a second treatment in the stent group was mostly caused by tumor overgrowth and migration of the Ultraflex stent. This stent, which is presently the most commonly used worldwide (35), was previously compared with the Flamingo Wallstent and Z stent in randomized trials. No clear differences were found in functional outcome, complication rate and incidence of recurrent dysphagia between these stent types (7, 36). Stent migration is still a frequently occurring problem, particularly for distally located tumors. The migration rate in our study was 18/108 (17%), which is in line with other studies (37, 38). The Ultraflex stent has an uncovered proximal and distal segment that allows the normal mucosa to project into the stent lumen. In the present study, the small diameter Ultraflex stent was used, however, larger diameter stents have been demonstrated to reduce migration, particularly if placed across the ogastro-esophageal junction (35).

The measurement of health related quality of life after palliative treatment for dysphagia is important for patients diagnosed with an incurable disease (20, 39). To obtain complete data on quality of life, all patients were regularly visited by a specialized nurse, since such patients are often not capable to fill out questionnaires due to the severity of the disease. The scores found in our study were in agreement with results from a study, in which quality of life was measured in patients undergoing various palliative treatments, using the same measures (39). On some scales, differences in health related quality of life became obvious more than 6 months after treatment with a benefit for brachytherapy. Our results highlight the importance of longitudinal data on quality of life using standardized measures in trials comparing curative or palliative treatment modalities for esophageal carcinoma.

We performed a detailed cost analysis (Table 3). We found that stent placement was initially more expensive than brachytherapy, due to the high purchase costs of the stent, but at the long term costs were comparable. Since this patient group often needs additional medical care due to the occurrence of complications and progressive disease, these initial costs were only a small part of the total medical costs. Therefore, costs considerations should not play an important role in the

decision on which of these two palliative treatments to use in patients with malignant dysphagia.

In conclusion, single dose brachytherapy is preferable to stent placement as the initial treatment for patients with progressive dysphagia due to inoperable carcinoma of the esophagus or gastro-esophageal junction. Stent placement may be reserved for patients with severe dysphagia in combination with a short life expectancy that need a more rapid relief of dysphagia or for persistent or recurrent tumor growth after brachytherapy. It remains to be studied, whether results of brachytherapy or stent placement can be improved by higher and/or fractionated radiation doses or by improved stent designs without jeopardizing safety.

APPENDIX

The Dutch SIREC study group consisted of:

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6B

Quality of life after palliative treatment for esophageal carcinoma – A prospective comparison between stent placement and single dose brachytherapy

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ABSTRACT

Background: Metal stent placement and single dose brachytherapy are commonly used treatment modalities for the palliation of inoperable esophageal carcinoma. We investigated generic and disease specific health-related quality of life (HRQoL) after these palliative treatments.

Methods: Patients with dysphagia from inoperable esophageal carcinoma were randomized to placement of a covered Ultraflex stent (n=108) or single dose (12 Gy) brachytherapy (n=101). We obtained longitudinal data on disease specific (dysphagia score, EORTC OES-23, visual analogue pain scale) and generic (EORTC QLQ-C30, EQ-5D) HRQoL at monthly home visits by a specially-trained research nurse. We compared HRQoL between the two treatments and analyzed changes in HRQoL during follow-up.

Results: Dysphagia improved more rapidly after stent placement than after brachytherapy, but long term relief of dysphagia was better after brachytherapy. For generic HRQoL, there was an overall significant difference in favor of brachytherapy on four out of five functional scales of the EORTC QLQ-C30 (role, emotional, cognitive and social) ($p<0.05$). Generic HRQoL deteriorated over time on all functional scales of the EORTC QLQ C-30 and EQ-5D, in particular physical and role functioning (on average -23 and -24 on a 100 points scale during 0.5 years of follow-up). This decline was more pronounced in the stent group. Major improvements were seen on the dysphagia and eating scales of the EORTC OES-23, in contrast to other scales of this disease specific measure, which remained almost stable during follow-up. Reported levels of chest or abdominal pain remained stable during follow-up in both treatment groups, general pain levels increased to a minor extent.

Conclusions: The effects of single dose brachytherapy on HRQoL compared favorably to those of stent placement for the palliation of esophageal cancer. Future studies on palliative care for esophageal cancer should at least include generic HRQoL scales, since these were more responsive in measuring patients' functioning and well-being during follow-up than disease specific HRQoL scales.

INTRODUCTION

Esophageal cancer is associated with a poor prognosis with a 5-year survival rate of around 10%(1, 2). More than 50% of patients with esophageal cancer have inoperable disease at presentation and the majority of these patients develop progressive dysphagia (3). Palliative treatments aim to relief dysphagia with minimal morbidity and mortality. Two widely used treatment modalities for palliation of malignant dysphagia include self-expanding metal stent placement (4-7) and single dose brachytherapy (8-11).

The preservation of health-related quality of life (HRQoL) is an important goal of palliative treatment, and therefore HRQoL should be an outcome measure in trials comparing palliative treatment modalities (12). In the majority of studies, relieve of dysphagia is the only aspect of HRQoL being measured although physical, mental, and social functioning and other esophageal cancer specific aspects of HRQoL are additional important outcome measures. HRQoL is commonly assessed by combining generic and disease specific measures. Various validated measures are available to assess generic HRQoL after cancer treatment (13, 14). In addition, measures for the assessment of disease specific HRQoL have been developed, and these have been suggested to be more specific for measuring differences in outcome between various treatment modalities for esophageal cancer (15).

We conducted a randomized trial comparing metal stent placement with single dose brachytherapy for the palliation of esophageal cancer. Longitudinal data on HRQoL before treatment and during follow-up were obtained. We compared these two treatment modalities with respect to generic and disease specific HRQoL. In addition, we determined the changes of HRQoL in patients with esophageal carcinoma during follow-up.

METHODS

Study population

Between December 1999 and July 2002, 209 patients with inoperable cancer of the esophagus or esophagogastric junction due to metastatic disease and/or a poor medical condition with progressive dysphagia were randomized to metal stent placement (n=108) or single dose brachytherapy (n=101).

Patients were treated with a covered Ultraflex stent (Boston Scientific, Natick, MA, USA) or a single dose of 12 Gy brachytherapy (intraluminal radiotherapy). Patients were included and treated in three university hospitals and six general hospitals in the Netherlands. The study was approved by the Central Committee on Research

Involving Human Subjects in The Netherlands. The results of this study in terms of clinical outcome (16) and costs (17) were reported previously.

Health related quality of life assessment

Disease specific quality of life was assessed with the dysphagia score (18), the esophageal cancer specific European Organization for Research and Treatment of Cancer (EORTC) OES-23 measure (15) and a visual analogue pain scale. Dysphagia was scored as follows: score 0: ability to eat a normal diet; score 1: ability to eat some solid food; score 2: ability to eat some semisolids only; score 3: ability to swallow liquids only; score 4: complete obstruction (18). The EORTC OES-23 measure determines disease specific HRQoL which is relevant to patients with esophageal carcinoma. It incorporates six multi-item scales (dysphagia, deglutition, eating, indigestion, chest/abdominal pain and emotional) and four single symptoms (having a dry mouth, troublesome taste, troublesome coughing and troublesome talking). The original measure has one extra symptom (hair loss). This item was removed because it was not applicable to the treatments under investigation. Before the start of the study, a Dutch translation was validated according to EORTC guidelines. Answer categories of the questions rang from 'not at all' (scored as 1) to 'very much' (scored as 4). We used a visual analogue pain scale consisting of a horizontal line of 10 cm in length on which patients were asked to score the severity of pain that they experienced, from 'no pain' to 'the most severe pain they could imagine'.

Generic HRQoL was assessed using the oncology-specific EORTC QLQ-C30 measure (14), and the EQ-5D (13) including an index score and a visual analogue scale (EQ-VAS) for self-rated health. The EORTC QLQ-C30 covers aspects of generic quality of life specific for cancer patients. The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health/quality of life scale. Various single symptoms are included as well. The scoring system is equivalent to the scoring system of the EORTC OES-23; answer categories on the questions rang from 'not at all' (scored as 1) to 'very much' (scored as 4). Scores on the items for the global health/quality of life scale rang from 1 ('very poor') to 7 ('excellent'). The EQ-5D assesses 5 dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, patients mark one of three levels of severity (level 1=no problems, level 2=some/moderate problems, level 3=severe/extreme problems), which subsequently

can be classified into one of 243 (3^5) possible health status profiles. Each profile can be linked to an index score based on empirical preferences for health status from an English general population sample (19). The EQ-VAS is a 20 cm vertical visual analogue scale on which patients are asked to rate their overall health between 0 ('worse imaginable health state') and 100 ('best imaginable health state').

Patients were prospectively followed by home visits of specially trained research nurses at 14 days, 1 month and then monthly until one year after treatment. After one year of follow-up, patients were visited every 3 months, and/or telephonic calls to the patient and the patients' practitioner were made until death. The EORTC OES-23, EQ-VAS, and visual analogue pain scale were filled out before treatment and during each home visit; the EORTC QLQ-C30 and EQ-5D were filled out before treatment, and 1, 3, 6, 9 and 12 months after treatment. The baseline HRQoL questionnaires were completed with help from one of the physicians or the principal investigator (MYVH), whereas questionnaires during follow-up were completed with help from the research nurses. Clinical baseline and follow-up data were obtained from all patients. The response of the quality of life measures was almost 95% during the entire follow-up period (in total 681/724 (94%) questionnaires were collected in the brachytherapy group and 717/752 (95%) in the stent group).

Statistics

Analyses were performed on an intention-to-treat basis. The occurrence of clinical endpoints was analyzed with Kaplan-Meier curves and log rank tests (16). The dysphagia scores at different time points between treatment groups were compared with a linear regression model that included the baseline dysphagia score to adjust for any pre-treatment differences between the groups. Time was included as a restricted cubic spline function, which was chosen because of its flexibility and smoothness (20). The interaction between time and treatment group was also included to allow for the presence of different time courses in the two groups.
The HRQoL measures were scored according to standard scoring algorithms to obtain scores for the various multi-item scales for the EORTC OES-23 (15) and EORTC QLQ-C30 (14) and the index and VAS scores for the EQ-5D (19). For the EORTC OES-23 and EORTC QLQ-C30 the crude scores for the individual items within a scale were first summed, and then divided by the number of items within the scale. Then, these scores were linearly transformed such that all scales ranged from 0 to 100 with a higher scale score representing a higher level of functioning. For the symptom scales and single symptoms of both measures, higher scores are

equivalent to a higher level of symptoms. For the EQ-5D index score and the EQ-VAS, higher scores represent a better health status. We compared quality of life scores of both treatments with analysis of repeated measurements(21). For each scale a model was fitted that included day and treatment group as fixed factors, and the baseline measure and interaction between day and treatment group as covariates. A simple compound symmetric covariance structure was assumed to hold for all scales.

For the analysis of the changes of HRQoL during follow-up, a model was fitted for each scale with time as linear factor. In case of interaction between both treatment modalities (with a p-value of <0.10), this model was fitted separately for each treatment, otherwise one model was fitted for the whole group. For the dysphagia and eating scale of the EORTC OES-23, two phases were described: an acute phase (< 30 days after randomization) and a chronic phase (> 30 days after treatment), as these scores did not follow a reasonable linear pattern in time. For each phase, a separate line was fitted. Calculations were performed with SPSS 10.1 (SPSS Inc., Chicago, IL, USA) and SAS 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical outcomes

The two patient groups were comparable with respect to their clinical characteristics (Table 1). Major complications during follow-up occurred more frequently after stent placement than after brachytherapy (28 in 27 patients (25%) vs. 14 in 13 patients (13%); p=0.02). Complications mainly consisted of bleeding (stent: 14 vs. brachytherapy: 5), perforation (2 vs. 2), fistula formation (6 vs. 3) and severe pain (3 vs. 1). Patients often needed additional treatment during follow-up for persistent or recurrent dysphagia, however, the number of patients needing re-treatment was not different between both groups (stent: 52 in 43 patients (40%) vs. brachytherapy: 53 in 43 patients (43%); p>0.20). Reasons for re-treatment after stent placement were mainly tumor recurrence (n=16), stent migration (n=18) and food bolus obstruction (n=16), and after brachytherapy tumor persistence (n=18) or tumor recurrence (n=26). Median survival was 155 (95% CI: 127-183) days after brachytherapy and 145 (95% CI: 103-187) days after stent placement (p>0.20).

Disease specific health related quality of life

The dysphagia score (18) improved more rapidly after stent placement than after brachytherapy. At 30 days after treatment, however, the dysphagia score was not

significantly different between stent placement and brachytherapy, and in the long term, the dysphagia score was better after brachytherapy (Figure 1).
The disease specific EORTC OES-23 scale scores showed overall significant differences in favor of brachytherapy on the dysphagia scale (p=0.009) and eating scale (p=0.003) both with a similar pattern (Figure 2). The other scales (deglutition, indigestion, retrosternal pain and emotional) did not show major differences between stent placement and brachytherapy, nor did the single symptoms of the EORTC OES-23. The visual analogue pain scale showed a trend towards less pain in the brachytherapy group (overall score: p=0.07) (Figure 3).
Scores on the dysphagia and eating scale of the EORTC OES-23 improved after both treatments during the first month of follow-up. After 1 month, scores on both scales deteriorated slowly during follow-up (Table 2, Figure 2). The scores on the deglutition scale, indigestion scale and pain scale of the EORTC OES-23 remained stable during follow-up in both treatment groups. Scores on the emotional scale (10 points on a 100 points scale during 0.5 years of follow-up in both treatment groups) and the different single symptoms (on average 8 points during 0.5 years of follow-up in the brachytherapy group vs. 13 points in the stent group) deteriorated to a moderate degree during follow-up. Experienced pain on the visual analogue pain scales increased only slightly during follow-up (+6 points during 0.5 years of follow-up in both groups; Table 2, Figure 3).

Table 1: Clinical characteristics of 209 patients randomized to brachytherapy or stent placement for palliation of dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction.

	Brachytherapy N=101	**Stent placement N=108**
Age (mean ± SD)	69 ± 13	69 ± 11
Male / Female	76/25	86/22
Tumor Histology		
Squamous cell carcinoma	29 (29%)	29 (27%)
Adenocarcinoma	69 (68%)	75 (69%)
Other	3 (3%)	4 (4%)
Dysphagia score before treatment	2.8 ± 0.9	2.8 ± 0.7

Table 2: Average changes in health related quality of life (HRQoL) during follow-up after brachytherapy (B) or stent placement (S) for palliation of dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction.

Scale	General population scores*	Mean baseline value	Changes in HRQoL during follow-up (per 0.5 year of follow-up) (95% CI)#	
			Total group of patients	Brachytherapy group (B) Stent group (S)
EORTC OES-23				
Dysphagia scale (0=best)				
< 30 days		58	-27 (-31 to -23)†	
> 30 days				B: 12 (8 to 16) S: 21 (16 to 25)
Deglutition scale (0=best)		12	2 (0.2 to 4)	
Eating scale (0=best)				
< 30 days		49	-13 (-17 to -9)†	
> 30 days				B: 11 (7 to 16) S: 21 (16 to 26)
Indigestion scale (0=best)		18	0.8 (-1 to 3)	
Pain scale (0=best)		21	2 (0.02 to 4)	
Emotional scale (100=best)		44	-10 (-12 to -8)	
EORTC QLQ-C30				
Physical functioning (100=best)	87	64		B: -18 (-23 to -12) S: -28 (-34 to -23)
Role functioning (100=best)	85	62		B: -19 (-25 to -12) S: -30 (-37 to -23)
Emotional functioning (100=best)	81	74	-6 (-9 to -2)	
Cognitive functioning (100=best)	88	83		B: -6 (-11 to -2) S: -16 (-20 to -11)
Social functioning (100=best)	87	76	-14 (-18 to -10)	
Global health/quality of life (100=best)	66	59		B: -7 (-12 to -3) S: -13 (-18 to -9)
Pain (0=best)	20	25	12 (9 to 16)	
Euroqol				
EQ-5D (100=best)	76	63	-21 (-27 to -16)	
Euroqol visual analogue scale (100=best)		59		B: -12 (-15 to -10) S: -16 (-19 to -14)
Visual analogue pain scale				
Visual analogue pain scale (0=best)		18	6 (4 to 8)	

* For the EORTC QLQ-C30 scores of a general German population (n=390) of men between 60-69 years are given (22). For the EQ-5D, scores of a general Swedish population (n=1321) of men and women between 60-69 years are given (23). Norm scores were not available for the EORTC OES-23 and visual analogue pain scale.

In case of interaction between treatment and time ($p<0.10$), we fitted a model for each treatment, in case of no interaction, the model was fitted for the total group of patients. A change of -10 means that HRQoL deteriorates with 10 points on a 100 point-scale during 0.5 years of follow-up.

† Change in HRQoL for 30 days of follow-up.

Figure 1: Dysphagia scores (scored on a scale from 0 (normal) to 4 (complete dysphagia)) in patients randomised to brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction. The symbols Δ and O represent mean dysphagia scores, the lines are spline functions with 95% confidence intervals.

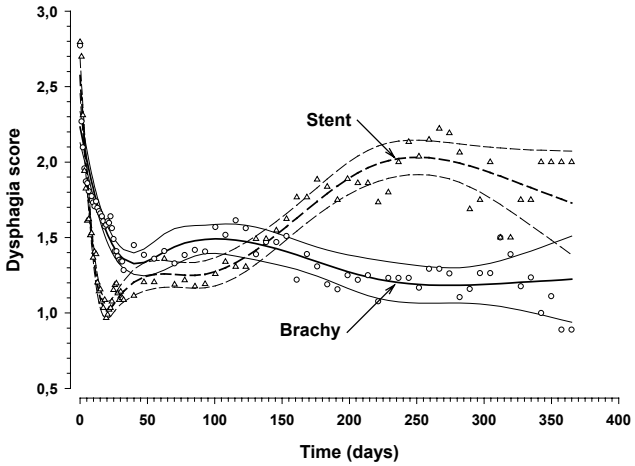


Figure 2: Dysphagia scale and eating scale of the disease specific EORTC OES-23 measure after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction. Graphs show the mean scores with 95% confidence intervals of the scales during follow-up. Higher scores represent more dysphagia or problems with eating.

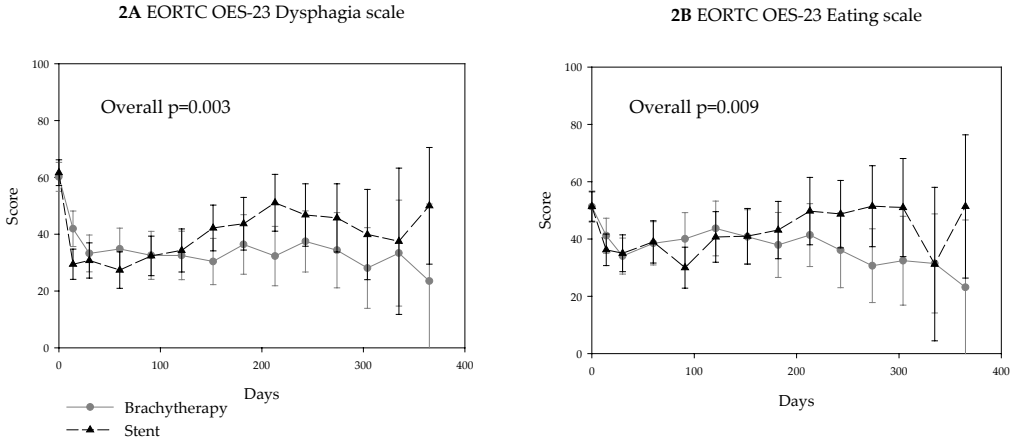
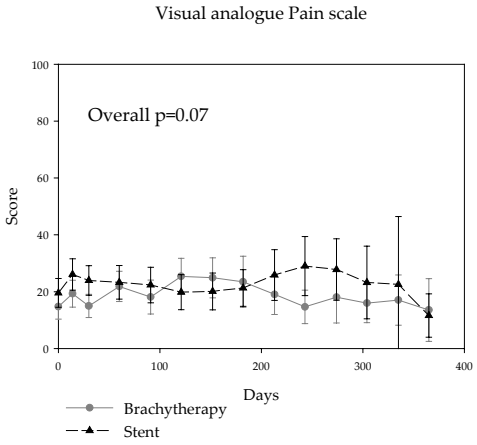


Figure 3: Self-reported pain level on the visual analogue pain scale after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction. Graphs show the mean scores with 95% confidence intervals of the scales during follow-up. Higher scores represent a higher level of pain.



Generic health related quality of life

There was an overall benefit for brachytherapy on the generic HRQoL measures over time. The EORTC QLQ-C30 scale scores showed an overall significant difference in favor of brachytherapy on four out of five functional scales including role functioning (p=0.05), emotional functioning (p=0.04), cognitive functioning (p=0.006), and social functioning (p=0.03) (Figure 4). This difference was most predominant at 6 months or later after randomization. Patients randomized to brachytherapy scored overall better on the single item dyspnea (p=0.003), and there was a trend towards fewer symptoms of fatigue and pain after brachytherapy (both p=0.07). The scores on the EQ-5D index and visual analogue scale for overall self-rated health were not significantly different for both treatments (Figure 5).

The generic HRQoL of our patient group with inoperable esophageal cancer was already lower before treatment compared to the general population (Table 2). Their generic HRQoL deteriorated further during follow-up on all functional scales of the EORTC QLQ-C30, in particular physical and role functioning (Table 2). This decline was more pronounced in the stent group than in the brachytherapy group (brachytherapy: -18 and -19 on a 100 points scale during 0.5 years of follow-up vs stent: -28 and -30 points for physical and role functioning, respectively). In addition,

Figure 4: Functional scales of the EORTC QLQ-C30 measure after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction. Graphs show the mean scores with 95% confidence intervals of the scales during follow-up. Higher scores represent a higher level of functioning.

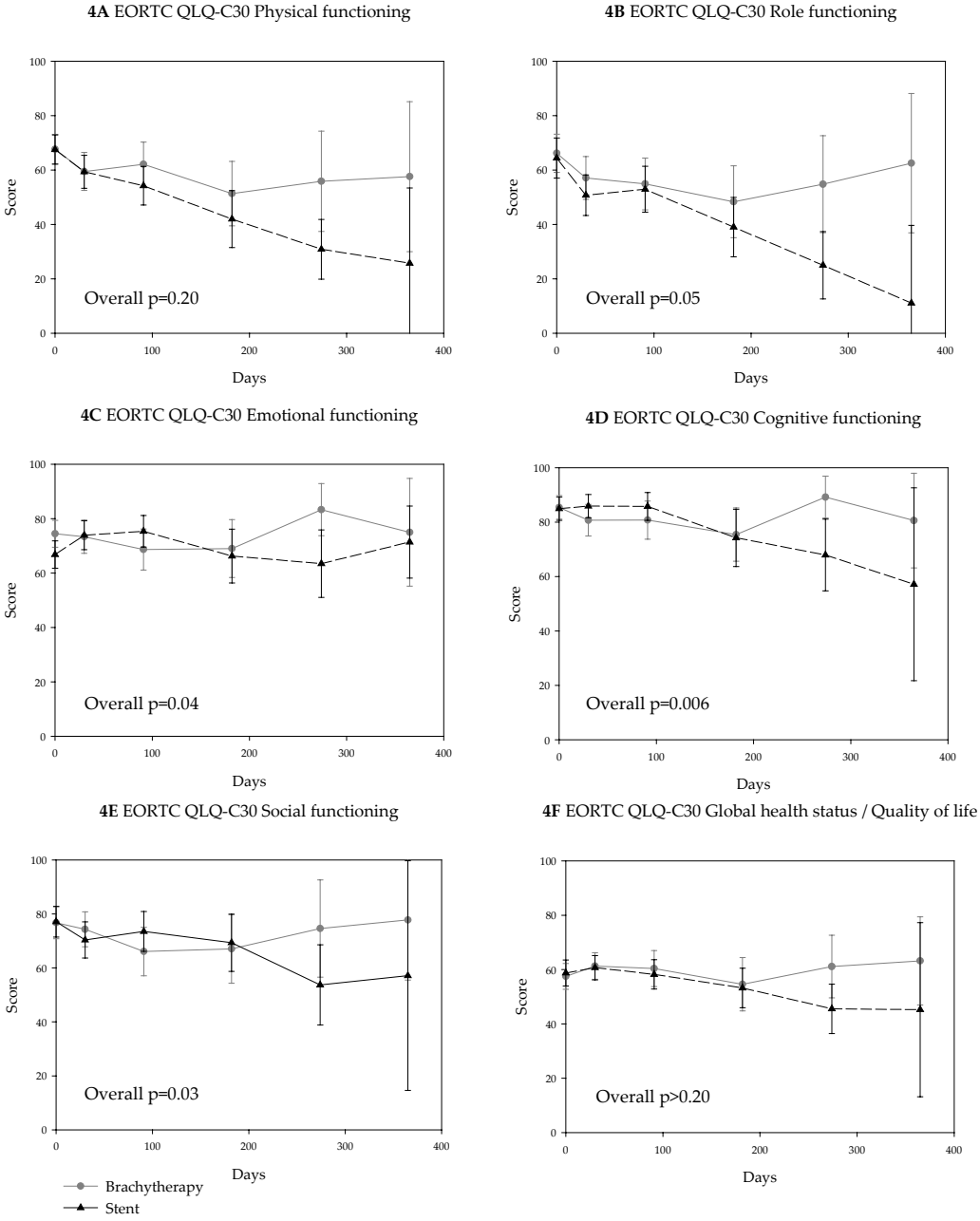
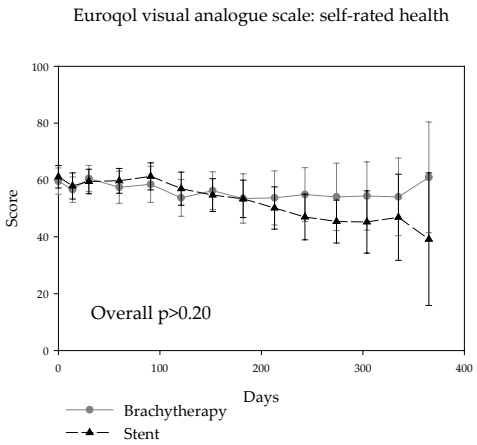


Figure 5: Euroqol visual analogue scale (EQ-VAS) for self-rated health after treatment with brachytherapy (n=101) or stent placement (n=108) for dysphagia due to inoperable carcinoma of the esophagus or esophagogastric junction. Graphs show the mean scores with 95% confidence intervals of the scales during follow-up. Higher scores represent a better self-rated health status.



the scores on the symptom scales and most single symptoms increased during follow-up (indicating a higher level of symptoms), in particular fatigue, dyspnea and appetite loss. Pain level on the EORTC QLQ-C30 increased during follow-up (+12 points during 0.5 years of follow-up in both groups; Table 2). We found no change in the symptom constipation/diarrhea and in financial difficulties during follow-up. Scores on the EQ-5D index and Euroqol visual analogue scale also declined during follow-up (Table 2).

DISCUSSION

This study provides a longitudinal prospective comparison of generic and disease specific HRQoL between two commonly used palliative treatments for esophageal cancer, i.e. single dose brachytherapy and stent placement. Although both treatments were effective in relieving dysphagia, treatment with single dose brachytherapy gave better overall scores on HRQoL scales compared to stent placement for the palliation of esophageal cancer. Most aspects of HRQoL deteriorated during follow-up in both treatment groups, however, the decline was more pronounced in the stent group.

Only a few studies have been published on HRQoL after palliative treatment for esophageal carcinoma (24-28). Palliative therapy in these studies included

placement of a plastic (25, 27, 28) or a metal stent (25, 26), laser therapy (24, 26, 27), external beam radiation (28) and chemoradiation (25). No studies have been published assessing HRQol after single dose brachytherapy for the palliation of malignant dysphagia. An overview of the results of these studies is shown in Table 3. From these studies, it can be concluded that although dysphagia scores improved after most of these palliative treatments, other aspects of HRQoL remained stable or deteriorated during follow-up. None of these studies however, made a comparison between two palliative treatments with respect to HRQoL, and patient numbers were small. Moreover, our study provides detailed longitudinal data with monthly assessments of HRQoL.

A variety of measures has been used in the reported studies to assess HRQoL after palliative treatment for esophageal carcinoma (24-28) (Table 3). In our study, we assessed disease specific HRQoL as well as generic HRQoL after brachytherapy and stent placement. We expected that the disease specific HRQoL measure (the EORTC OES-23) would have been the one that was most responsive to differences between the two treatments and changes in HRQoL during follow-up. The separately scored dysphagia scores (18) and the dysphagia scale of the EORTC OES-23 followed a similar pattern over time, consisting of a rapid improvement after treatment and a slow deterioration of dysphagia scores during follow-up. In line with this, the eating scale showed a similar pattern. However, all other scales of the EORTC OES-23 did not reveal differences between the two treatments. In addition, most of these scales remained stable during follow-up. In contrast, several aspects of generic HRQoL differed between the two treatments, becoming even more evident after 6 months of follow-up. Generic HRQoL deteriorated during follow-up, and this decline was more pronounced after stent placement. Therefore, we consider the generic HRQoL measures (in particular the EORTC QLQ-C30) more responsive in measuring patients' functioning and well-being during follow-up than the disease specific EORTC OES-23.

Recently, the EORTC OES-23 has been revised to a measure with 18 questions. This revised EORTC OES-23 was recently validated in a large cohort of patients (29). In this revised measure, the emotional scale and the single item 'hair loss' were removed, whereas the indigestion scale now consists of 2 instead of 3 items. The authors recommended the new EORTC OES-18 as a valuable addition to the EORTC QLQ-C30 for patients with esophageal cancer. However, since only the dysphagia and eating scales showed differences in the EORTC OES-23 and these items can effectively be measured with the separate dysphagia score, we consider it sufficient to use the EORTC QLQ-C30 in combination with the separate dysphagia score to obtain complete HRQoL data in patients with inoperable esophageal carcinoma.

In our study we also used the EQ-5D for generic HRQoL. This measure provides a single index value, which is easy to use for cost-effectiveness calculations, and is

therefore advisable in case a cost-effectiveness analysis will be performed. A detailed cost calculation of our study was reported previously (17).

For the interpretation of the HRQoL in our patient group and the differences during follow-up, it is interesting to compare HRQoL in our patient group with inoperable esophageal cancer to HRQoL in the general population. Norm scores of the general population were available for the EORTC QLQ-C30 (22) and the EQ-5D (23). We are not aware of norm scores of the EORTC OES-23 and the visual analogue pain scale. As expected, the scores on all scales of our study population at baseline were lower compared to the available scores of the general population (22, 23) (Table 2). In particular, substantial differences were noted for physical and role functioning, as well as for the EQ-5D. This stresses the importance of preservation of the already diminished HRQoL in patients with esophageal cancer needing palliative treatment.

Pain is an important issue of HRQoL after palliation. In our study, pain was assessed using various pain scales, i.e., the pain scale of the EORTC OES-23, which measures pain while eating, chest pain and abdominal pain, the pain scale of the EORTC QLQ-C30, which measures pain in general, and a visual analogue pain scale on which patients could rate their experienced level of general pain. Pain level on the EORTC OES-23 (both chest pain and abdominal pain) remained stable during follow-up in contrast to general pain, which increased moderately on both the EORTC QLQ-C30 and the visual analogue pain scale (Table 2). The three pain scales had similar baseline scores of, on average, 20 points on a 100-points scale, which was reported previously as well (25). Chest or abdominal pain might well be the result of the palliative treatment itself. In our experience, this pain usually diminishes or disappears a few days to one week after the procedure. Although the pain scale of the EORTC OES-23 is not a measure for acute post-treatment pain (the first follow-up visit was at 14 days after treatment), the scores indicate that chest or abdominal pain was not a problem during follow-up. During follow-up more than 50% of our patients needed narcotic analgesics. In most patients, this is probable due to progression the disease rather than a result of the palliative treatment. The reported pain levels on the EORTC QLQ-C30 and the visual analogue pain scale only moderately increased during follow-up. This indicates that pain management was adequate during follow-up.

In conclusion, treatment with single dose brachytherapy gave better overall scores on HRQoL scales compared to stent placement for the palliation of esophageal cancer. Major improvements were seen on the dysphagia and eating scales of the disease specific EORTC OES-23, in contrast to other scales of this disease specific measure, which remained almost stable during follow-up. In addition, pain levels remained stable or increased to a minor extent during follow-up, indicating that adequate pain management during follow-up is important. Future studies on palliative care for esophageal cancer should at least include generic HRQoL scales,

since these were more responsive in measuring patients' functioning and well-being during follow-up than disease specific HRQoL scales.

APPENDIX

The Dutch SIREC study group consisted of:
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Special thanks to the dedicated work of the research nurses: Joke Moerman, Alice M. Froeling, Hannie van Ginkel-Welmers, Corine A. van Poortvliet-de Ruiter, Liesbeth E. Boon and Netty M. Mouthaan, and to Coleta Verheij from the Trial Office of the Department of Oncology, Erasmus MC Rotterdam.

Tabel 3: Overview of studies investigating health related quality of life (HRQoL) after palliative treatment for esophageal cancer.

Author	N	Treatment	HRQoL measures	Follow-up measurements	Major conclusions
Barr et al. 1991(24)	40	Laser	Dysphagia score Linear analogue self-assessment (LASA) Physician's assessment using a quality of life index (QLI)	Monthly until death	Dysphagia score improved LASA and QLI were improved at some time after laser therapy
Loizou et al. 1992(27)	38	Laser n=15 Plastic tube n=23	Dysphagia score Linear analogue self-assessment (LASA) Physician's assessment using a quality of life index (QLI)	Various times (not further specified) until death	Dysphagia score improved LASA + QLI scores improved after treatment but deteriorated during follow-up
O'Hanlon et al. 1995(28)	43	Plastic tube Radiotherapy	Dysphagia score Rotterdam symptom checklist Measure on activities on daily living	6 and 16 weeks	Dysphagia improved Other HRQoL parameters remained stable or deteriorated
Blazeby et al. 2000(25)	37	Plastic/Metal stent n=30 Chemoradiotherapy n=7	EORTC QLQ-C30 EORTC OES-24 (only dysphagia scale)	Monthly until death	Most aspects of HRQoL remained stable during follow-up
Dallal et al. 2001(26)	65	Laser n=34 Metal stent n=31	Dysphagia score Hospital Anxiety and Depression questionnaire Short Form 36 EORTC QLQ-C30 EORTC OES-24	1 month	Dysphagia scores were not improved after both treatments. Laser group: other HRQoL scores remained stable Stent group: other HRQoL scores had deteriorated at 1 month after treatment
Present series	209	Brachytherapy n=101 Metal stent n=108	Dysphagia score EORTC QLQ-C30 EORTC OES-23 EQ-5D Visual analogue pain scale	14 days, then monthly until death	Dysphagia scores improved after both treatments. Scores on the EORTC QLQ-C30 and EQ-5D deteriorated in both groups but more in the stent group. Scores on the EORTC OES-23 improved or remained stable

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6C

Cost study of metal stent placement versus single dose brachytherapy in the palliative treatment of esophageal cancer

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ABSTRACT

Self-expanding metal stent placement and single dose brachytherapy are commonly used for the palliation of esophageal obstruction due to inoperable esophagogastric cancer. We randomized 209 patients to placement of an Ultraflex stent (n=108) or single dose brachytherapy (12 Gy, n=101). Costs comparisons included comprehensive data of hospital costs, diagnostic interventions and extramural care. We acquired detailed information on health care consumption from a case record form and from monthly home visits by a specialized nurse.

Initial costs of stent placement were higher than the costs of brachytherapy (€1,500 vs. €570; $p<0.001$). Total medical costs were however similar (stent €11,195 vs. brachytherapy €10,078, $p>0.20$). Total hospital stay during follow-up was 11.5 days after stent placement versus 12.4 days after brachytherapy, which was responsible for the high intramural costs in both treatment groups (stent: €6,512 vs. brachytherapy: €7,982, $p>0.20$). Costs for medical procedures during follow-up were higher after stent placement (stent: €249 vs. brachytherapy: €168, $p=0.002$), while the costs of extramural care were similar (€1,278 vs. €1,046, $p>0.20$).

In conclusion, there are only small differences between the total medical costs of both palliative treatment modalities, despite the fact that the initial costs of stent placement are much higher than those of brachytherapy. Therefore, cost considerations should not play an important role in decision making on the appropriate palliative treatment strategy for patients with malignant dysphagia.

INTRODUCTION

The incidence of esophageal cancer has risen rapidly, due to a marked increase in the incidence of adenocarcinoma (1, 2). Esophageal cancer is a disease with a high mortality, as reflected by a 5-year survival of 10-15% (3). Moreover, more than 50% of patients with esophageal cancer have already inoperable disease at presentation. Most of these patients require palliative treatment to relieve progressive dysphagia (4). Treatment options presently available for palliation of dysphagia include self-expanding metal stent placement (5-7), laser therapy (8), photodynamic therapy (PDT) (9, 10), external beam radiation in combination with brachytherapy (11, 12), brachytherapy as a sole treatment (13-15), and dilatation (16). A disadvantage of laser therapy is that repeated treatment sessions are required to achieve and maintain adequate palliation (8, 17). A combined treatment of external beam radiation with brachytherapy is often too intensive for patients with inoperable disease due to metastases or a poor medical condition. PDT involves the local destruction of tumor tissue by light of a specific wavelength activating a previously administered photosensitizer which is retained in malignant tissue. Due to the high costs of the treatment, the side effects and the necessity of repeated treatments every 6-8 weeks, PDT is not considered to be the most optimal treatment for palliation of malignant dysphagia (18). Dilatation can relieve dysphagia temporarily, but it often provides relief palliation for a short period. In many patients with inoperable disease, a stent is placed for the palliation of dysphagia. In addition, brachytherapy as a sole treatment is frequently used in Western Europe, South Africa, Japan and to a lesser extent in the USA. Both stent placement and brachytherapy have been proven to be effective in relieving dysphagia with a low complication rate, but recurrent dysphagia due to various causes is seen in 30-40% of patients (13, 15, 19).

In order to comprehensively assess the relative merits of the different palliative treatments of malignant dysphagia, health economic aspects should be incorporated. Remarkably, the economic implications of both stent placement and brachytherapy have been evaluated only in a few studies(8, 20-23). If costs were considered, these were only 'roughly' calculated (8), using charges/fees and with little information about the differentiation of the costs. In addition, the number of patients incorporated in the studies was low (8, 21, 23). In studies on costs this may result in a high degree of distortion, because peaks in volumes of some expensive cost items can highly influence the average outcomes.

We aimed to study the total direct and indirect costs of brachytherapy and stent placement in the palliation of malignant dysphagia within the framework of a

randomized trial. We present estimates of the full cost price, based on real resource use, in substantial patient groups.

MATERIALS AND METHODS

Study population

We performed a prospective study in 3 university hospitals and 6 general hospitals in the Netherlands. Between December 1999 and July 2002, 209 consecutive patients with dysphagia from inoperable carcinoma of the esophagus or gastric cardia due to metastases and/or a poor medical condition were randomized to placement of a covered Ultraflex stent (n=108) or single dose (12 Gy) brachytherapy (n=101). For brachytherapy, a flexible applicator (Bonvoisin-Gérard Esophageal Applicator, Nucletron, Veenendaal, The Netherlands) with a diameter of 10 mm was passed down the esophagus. A single dose of 12 Gy was administered with the radioactive source ^{192}Iridium at 1 cm from the source axis of the applicator. The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands.

Study endpoints

Clinical outcomes were functional outcome, complications, persisting or recurrent dysphagia needing re-intervention, survival and quality of life, as measured by standardized questionnaires. The clinical outcomes have been presented in detail elsewhere (24, 25). Here, we will focus on the real medical costs of the two treatment strategies. Costs were studied from a societal perspective and were estimated for the period after randomization until death for 95% of the patients or follow-up of at least 9 months for the remaining 5% of patients.

Follow-up

Patients were prospectively followed by home visits of specially trained research nurses at 14 days, 1 month and then monthly until one year after treatment. After one year, patients were visited every 3 months, and/or telephone calls to the patient and/or the patients' general practitioner were made. For each patient, we registered the number of inpatient days, the time needed for nursing care and therapy as well as the visits to physicians and other health practitioners by a checklist filled in by the research nurse. The response was more than 90% during the entire follow-up period. The participating clinicians filled out standardized case record forms (CRFs) during control visits, re-treatments and admissions.

Cost calculations

Real medical costs were calculated by multiplying the volumes of health care use with the corresponding unit prices. We made a distinction between the full cost price of the interventions brachytherapy and stent placement by itself and the total medical costs per patient during follow up.

The calculation of the full cost price of brachytherapy and stent placement consisted of detailed measurement of investments in manpower, equipment, materials, housing and overhead. The salary schemes of hospitals and other health care suppliers were used to estimate costs per hour for each caregiver. Taxes, social securities and vacations were included, as well as the costs of the time that could not be assigned to other patients. The costs of equipment included those of depreciation, interest and maintenance.

For the calculation of the total medical costs per patient, we distinguished intramural medical costs (inpatient days, health practitioner activities, the full cost price of the medical treatment and other medical procedures) and extramural medical costs (home care, general practitioner). Costs caused by loss of production due to absence from work were not taken into account, because the majority of patients were retired from work.

For the most important cost items, unit prices were determined by following the micro-costing method (26), which is based on a detailed inventory and measurement of all resources used. For instance, we registered time investments of health practitioners per patient (during the intervention). Costs for inpatient days in hospital were estimated as real, basic costs per day using detailed information from the financial department of the hospital. We made a distinction between the costs of general and university hospitals. These estimates included overhead and indirect costs. From a differential point of view, i.e. comparison of the two treatment strategies, some diagnostic interventions were decided to be less relevant. We chose not to invest much time and effort in exploring costs that were unlikely to make any difference to the study result (27), for example because they were low in price or volume. For these items we used charges as a proxy of real costs. In the Netherlands a detailed 'fee for service' system is used for the remuneration of medical interventions and diagnostic procedures. In order to calculate for the costs for medication, we used average charges for analgesics, antibiotics, and additional medications.

Table A (appendix) gives an overview of the cost categories and data used in the cost calculations. We reported costs in Euro for the year 2002, when 1 Euro

equalized approximately 1 US dollar. Discounting was not relevant because of the limited time horizon (median survival 4-5 months).

Statistical analysis

All analyses were performed on an intention-to-treat basis. The cost differences between brachytherapy and stent placement were analyzed using the Mann-Whitney U test. Since cost data per patient (but not per day care) are typically highly skewed, we used non-parametric bootstrap techniques to derive a 95% confidence interval for the differences in distributions of the direct medical costs.
In a sensitivity analysis the effect of excluding 'palliative related costs' was assessed by leaving these costs out of consideration. We performed calculations assuming that nursing home admissions and nursing care at home were not directly related to both treatments, but could be attributed to the advanced stage of the disease.

RESULTS

Patient characteristics and clinical outcomes

The two patient groups were comparable with respect to patient and tumor characteristics. Both treatment groups consisted predominantly of males, with a mean age of 69 year (Table 1).

Dysphagia improved more rapidly after stent placement than after brachytherapy. However, overall improvement of dysphagia was better after brachytherapy. More complications occurred after stent placement (33% total complications versus 21% after brachytherapy; p=0.02). Major complications within 7 days after treatment included perforation (n=3), fever (n=2), severe pain (n=2) and aspiration pneumonia (n=2). Late major complications consisted predominantly of hemorrhage (n=19) occurring more frequently after stent placement (14 versus 5 after brachytherapy). The need for re-intervention for persistent or recurrent dysphagia was not significantly different for both groups (40% vs. 43%, respectively). Recurrent dysphagia after stent placement was predominantly caused by tumor overgrowth (n=16), stent migration (n=18) or food bolus obstruction (n=16), and was treated by placement of a second stent, endoscopic stent clearance or a variety of other treatments. The majority of re-interventions after brachytherapy were caused by tumor persistence (n=18) or tumor recurrence (n=26), both most frequently treated with placement of a stent.

Median survival was similar for both treatment groups (stent: 145 vs. brachytherapy: 155 days). There was an overall longterm benefit in general (EORTC QLQ C-30 and EuroQol-5D) and disease-specific quality of life scores (EORTC OES-23) in the brachytherapy group during follow-up.

Table 1: Characteristics of 209 patients randomized to brachytherapy or stent placement for palliation of malignant dysphagia

	Brachytherapy N=101	**Stent placement N=108**
Age	69+/-13	69+/-11
Gender (male/female)	76/25	86/22
WHO performance score before treatment (mean +/- SD)	1.0+/-0.4	0.9+/-0.5
Indications for treatment		
Metastases	66 (65%)	68 (63%)
Poor medical condition	23 (23%)	28 (26%)
Both	12 (12%)	12 (11%)
Tumor length (cm) (mean +/- SD)	7.5 +/- 2.6	7.5 +/- 2.8
Received assigned intervention	96 (brachytherapy)	105 (stent)
Re-intervention	45 (stent)	2 (brachytherapy)
	3 (2nd brachytherapy)	24 (2nd stent)
Median survival (days)	155 (95% CI: 128-182)	145 (95% CI: 104-186)
Total complications	23 in 21 patients (21%)	45 in 36 patients (33%)
Major complications	14 in 13 patients (13%)	28 in 27 patients (25%)
Minor complications	8 in 8 patients (8%)	16 in 16 patients (15%)
Persistent/recurrent dysphagia	53 in 43 patients (43%)	52 in 43 patients (40%)

Costs

The initial cost price of treatment, based on real resource use, was much higher for stent placement (€1,500) than for brachytherapy (€570). The main cause for this difference was the high purchase costs of the Ultraflex stent (€1,100) (Table 2).
Table 3 gives an overview of the average health care use and costs per patient for stent placement and brachytherapy. Patients randomized to brachytherapy were admitted on average 7.1 days longer in a health care institution than patients randomized to stent placement (23.4 versus 16.3 days). The main reason for this was the longer period patients randomized to brachytherapy were admitted to nursing homes (11.0 versus 4.6 days). The average time spent in hospital was similar for both treatments (12.4 for brachytherapy and 11.5 for stent placement). The costs for intramural care were by far the highest cost category for both treatments, but differences were not statistically significant (stent placement €6,512 vs. brachytherapy €7,982, p>0.20). Costs of medical procedures during follow up were significantly higher for stent placement (€249) than for brachytherapy (€168) (p=0.002), since major complications and re-interventions occurred more often after stent placement than brachytherapy. The average costs for extramural care were €1,278 for brachytherapy and €1,046 for stent placement. For both treatments, this could largely be attributed to home visits by the general practitioner and specialized nursing care at home. The costs for medications were similar for brachytherapy and stent placement (€350 and €325).
The total average costs per patient for both treatments were similar at €11,195 for brachytherapy and €10,078 for stent placement (p>0.20). If the 'palliation related' health care was not taken into consideration, then the costs of intramural and extramural care for brachytherapy and stent placement decreased. This resulted in total medical costs for brachytherapy of €8,490 and for stent placement of €8,538 (p>0.20).

Table 2: Full cost price (€, 2002) of brachytherapy and stent placement

Cost category	**Brachytherapy**	**Stent placement**
Personnel	152	74
Equipment	75	40
Materials	14	1307
housing/overhead	70	40
Diagnostics	259	37
Total costs	**570**	**1500**

Table 3: Average health care use and costs (€, 2002) per patient for stent placement and brachytherapy

Cost category		Brachytherapy (n=101)		Stent placement (n=108)		p-value[1]
	Cost price	Volume	Costs	Volume	Costs	
Treatment						
Brachytherapy	570	0.96	547	0.019	11	
Stent placement	1500	0.58	870	1.29	1935	
			1417		1946	p<0.001
Intramural care						
inpatient days						
hospital (academic)	520	7.7	4006	6.9	3587	
hospital (general)	381	4.7	1788	4.6	1760	
ICU	1450	0.02	31	0.06	72	
nursing home	173	11	1898	4.8	838	
health practitioner (inpatient)						
physician (academic)	135	1.41	190	1.30	176	
physician (general)	98	0.70	69	0.82	79	
			7982		6512	p>0.20
Medical procedures						
Endoscopy	125	0.74	93	1.17	146	
PEG	100	0.04	4	0.04	4	
X-ray thorax	37	0.78	29	1.41	52	
X-ray abdomen	37	0.07	3	0.21	5	
Ultra-sound abdomen	42	0.05	3	0.04	2	
X-ray esophagus	37	0.13	5	0.19	7	
ERT	39	0.81	32	0.57	22	
Adjustment ERT	98	0.15	15	0.09	9	
			168		249	p=0.002
Extramural care						
general practitioner (inpatient)	19	0.9	18	1.06	20	
general practitioner (home visit)	37	9	333	8.1	298	
nursing care at home (specialized)	55.6	13.4	750	11.4	638	
nursing care at home	32.4	1.9	61	2	64	
drip-feed	8.5	13.7	116	3.05	26	
			1278		1046	p>0.20
Medication			350		325	
Total costs per patient			**11195**		**10078**	**p>0.20**

[1] derived from 2000 bootstrap samples drawn with replacement.

DISCUSSION

We found only small differences between the total medical costs of single dose brachytherapy as compared to metal stent placement for the palliation of dysphagia from inoperable esophageal carcinoma. Stent placement was initially more expensive than brachytherapy, due to the high purchase costs of the stent, but at the long term costs were comparable.

Many patients in both treatment groups needed re-intervention for persistent or recurrent dysphagia. Of the patients randomized to brachytherapy, 45/101 (45%) subsequently received a stent, while 24/108 (22%) of the patients randomized to stent placement received a second stent during follow-up. Since our analysis was based on the intention-to-treat principle, costs of non-assigned treatment were accounted to the randomized treatment group. Total treatment costs, which included the average costs of additional treatment plus re-intervention, were higher for stent placement. However, if the intramural and extramural health care costs were also taken into account, then these high initial costs were only a small part of the total medical costs, which resulted in similar total medical costs.

Cost comparisons between medical treatments are often based only on the initial costs. This would imply that stent placement, with the high purchase costs of the device, would be less attractive than brachytherapy. In this study, we clearly demonstrated that total medical costs of stent placement and brachytherapy were similar when the full follow-up period was considered. This illustrates that cost comparisons between interventions may vary substantially depending on which, and how many, components are included in a total cost equation (28).

Few studies have been published on costs of brachytherapy or stent placement in the palliative treatment of esophageal cancer. Three studies compared stent placement with plastic endoprostheses (23), conventional therapy (22) or thermal ablative therapy (8). These three studies reported corresponding initial costs for stent placement, but found lower total medical costs, compared to our study. Dallal et al. (8) included only the costs of the intervention and hospital stay in the total costs for stent placement (€4,920), which can explain the difference in total costs compared to our study. They found a median hospital stay of 12 days after stent placement, similar to findings in our study (Table 3). Farndon et al. (21) compared the placement of a plastic endoprosthesis with single dose brachytherapy and showed that the total costs of brachytherapy (€2,603) were lower compared to stenting (€3,564). Presently, plastic endoprostheses are no longer considered adequate for palliation of malignant dysphagia due to a high procedure-related complication rate with plastic endoprostheses (29). Since there is no detailed

information available on the costs in the above-mentioned articles (8, 21-23), it is not possible to explain the differences in total costs between these studies and ours. It could well be that both intramural and extramural health care use was underreported. Finally, the number of patients included and receiving stent placement or brachytherapy was relatively low (n<35) in all these studies (8, 21-23).

A common problem when using clinical trials for any kind of cost assessment arises from the fact that the clinical protocol mandates more visits, consultations, and examinations than otherwise used in clinical practice (30). For a treatment in a research setting there will be more costs, compared to daily practice. Therefore, we excluded protocol driven medical care such as visits of the nurses from our cost calculation. The main goal of these visits was, apart from giving advice to patients, registration of health care consumption and outcomes, which is, of course, not common practice in normal daily care of patients.

Despite the high costs involved, detailed cost studies in the treatment of malignant disease and palliative therapy have received little attention. This may be due to the inherent difficulties in performing such studies. Follow up of patients with malignant disease is sometimes difficult since the mortality rate is high, particularly among patients receiving palliative therapy (31). In a palliative setting it is sometimes difficult to differentiate between health care consumption which can be attributed to the palliative stage of the disease or only to the treatment modality. If palliation related costs were excluded, we found a decrease of total costs of both treatments but this did not affect the final conclusion that the total costs for brachytherapy and stent placement were similar.

This study focused on costs and not on efficiency. The primary aim of both treatments is to palliate symptoms rather than to improve survival of esophageal cancer. Both treatments resulted in an improvement of an important symptom of inoperable esophageal cancer, i.e. dysphagia. As survival of the two treatment groups was comparable, we did not perform a formal cost-effectiveness analysis. Despite a less rapid relief of dysphagia and a higher initial failure rate, brachytherapy was found to be an attractive alternative to stent placement in the palliation of malignant dysphagia, as brachytherapy was safer with fewer procedures needed for recurrent dysphagia (24).

In conclusion, our study provides detailed insight in the total medical costs of two frequently used palliative treatments of dysphagia due to esophageal cancer, i.e., stent placement and brachytherapy. In spite of the higher initial costs for stent placement than for brachytherapy, total medical costs were similar. Therefore, cost

considerations should not play an important role in decision making on the appropriate treatment strategy.

APPENDIX

The Dutch SIREC study group consisted of:
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APPENDIX

Table A: cost categories and data used in cost calculations

cost category	Parameter	Data collection volume of care		Cost estimate
		CRF (physician)	Questionnaire (nurse)	(unit price)
Treatment				
Brachytherapy	Number	*		Real costs
Stent placement	Number	*		Real costs
Inpatient days				
Hospital (academic)	Days	*	*	Real costs
Hospital (general)	Days	*	*	Real costs
ICU	Days	*	*	Real costs
Nursing home	Days		*	Charges
Health practitioner (inpatient)				
Physician (academic)	Visits	*	*	Real costs
Physician (general)	Visits	*	*	Real costs
Medical procedures				
Endoscopy	Number	*		Real costs
PEG	Number	*		Charges
X-ray thorax	Number	*		Charges
X-ray stomach	Number	*		Charges
Ultra-sound scan stomach	Number	*		Charges
X-ray esophagus	Number	*		Charges
ERT	Number	*		Charges
other therapy	Number	*		Charges
Extramural care				
General practitioner (inpatient)	Visits		*	Fees
General practitioner (home visit)	Visits		*	Fees
Nursing care at home	Number		*	Charges
Nursing care at home (specialized)	Number		*	Charges
Drip-feed	Days		*	Charges

7

Future Developments

7

Esophageal stents with anti-reflux valve for tumors involving the distal esophagus and gastric cardia: a randomized trial

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ABSTRACT

Background: Self-expanding metal stents deployed across the gastroesophageal junction predispose to gastroesophageal reflux. We assessed the efficacy of the FerX-Ella stent with an anti-reflux mechanism in preventing gastroesophageal reflux.

Methods: Between April 2002 and May 2003, 30 patients with carcinoma of the distal esophagus or gastric cardia were randomized to receive either a FerX-Ella stent with a windsock-type anti-reflux valve (n=15) or a standard open FerX-Ella stent (n=15). Gastroesophageal reflux was assessed by standardized questionnaires and 24-hr pH monitoring 14 days after treatment.

Results: Technical problems during placement occurred in 3 patients caused by stent migration (n=2) and a problem with the introducing system (n=1). Dysphagia improved from a median score of 3 (liquids only) to 1 (eat some solid food) in the anti-reflux group and from 3 to 0 (solid foods) in the open stent group ($p>0.20$). Reflux symptoms were reported by 3/12 (25%) patients with an anti-reflux stent and by 2/14 (14%) patients with an open stent. The 24-hr pH monitoring succeeded in 11 patients, with increased esophageal acid exposure for both types of stents (median 24-hr reflux time: anti-reflux stent (n=9): 23% vs. open stent (n=2): 10% (normal: <4%); p=NS). Major complications were the same in patients with anti-reflux stents or open stents, 3 (20%) in each group, consisting of bleeding (n=3), severe pain (n=2), and aspiration pneumonia (n=1). The main cause of recurrent dysphagia was stent migration in 7/30 (23%) patients.

Conclusions: The FerX-Ella stent provides symptomatic relief against malignant dysphagia, however its anti-reflux valve failed to prevent gastroesophageal reflux.

INTRODUCTION

Annually approximately 400,000 patients are diagnosed worldwide with esophageal cancer and over 350,000 die of this malignancy. This makes esophageal cancer the eighth most common cancer, and sixth on the list of cancer mortality causes (1). The incidence of esophageal carcinoma has risen noticeably over the past two decades in both the USA and Western Europe, due to a marked increase in the incidence of adenocarcinoma (2, 3). The prognosis of esophageal cancer is poor with a 5-year survival of 10-15% (4, 5). In practice, over 50% of patients with esophageal cancer already have inoperable disease at presentation with the majority requiring palliative treatment to relieve progressive dysphagia (6). Covered self-expanding metal stents have become popular for this indication (7-10).

Currently, there are several main types of self-expanding stents available: 1) the Ultraflex stent (Microvasive/Boston Scientific Corp., Watertown, MA), 2) the Wallstent (Microvasive/Boston Scientific Corp.) with a recently introduced new design, the Flamingo Wallstent, 3) the Z stent (Wilson-Cook Europe A/S, Bjaeverskov, Denmark) with a Korean modification, the Choo stent (M.I. Tech, Seoul, Korea), and 4) the plastic Polyflex stent (Rüsch GmbH, Kernen, Germany) (7-10). We recently demonstrated that the Ultraflex stent, the Flamingo Wallstent and the Z stent afforded a similar degree of relief of dysphagia from inoperable cancer of the esophagus or gastric cardia. Moreover, the occurrence of complications and recurrent dysphagia was similar between these three stent types (11).

As the incidence of adenocarcinoma of the distal esophagus is rising rapidly (2, 3), there is likely to be an increasing deployment of metal stents across the gastroesophageal junction. In this situation, the benefits of using metal stents can be limited by their predisposition to cause gastroesophageal reflux.

Recently, stents have become available that incorporate an anti-reflux mechanism. Studies have reported efficacy of these types of stents *in vitro*, in an animal model, as well as in patients (12-16). These studies showed that patients treated with an anti-reflux stent had fewer symptoms of gastroesophageal reflux than patients with a standard open stent. However, no clinical trial has yet been performed comparing anti-reflux stents with open stents of the same design. In addition, the efficacy of the anti-reflux design was only assessed by patient interviews and not objectively studied by 24-hour pH monitoring.

The aim of the present study was to evaluate the effectiveness of a new type of self-expanding metal stent for palliating malignant dysphagia from carcinoma of the distal esophagus or gastric cardia, the FerX-Ella stent with an anti-reflux mechanism (Ella-CS, Hradec Kralove, Czech Republic), in preventing gastroesophageal reflux

by comparing it with the same type of metal stent without anti-reflux mechanism. The degree of reflux in both stents was assessed by patient interviews at several time points and by 24-hour pH monitoring at 14 days after stent placement.

PATIENTS AND METHODS

From April 2002 until May 2003, 30 consecutive patients with dysphagia caused by inoperable carcinoma of the distal esophagus or gastric cardia were randomized to placement of a FerX-Ella stent with anti-reflux valve (n=15) or a standard open FerX-Ella stent (n=15). Patients were blinded for the type of stent they received. Exclusion criteria were a tumor length of more than 12 cm, an esophagorespiratory fistula, or previous stent placement.

Before randomization, patients were stratified for location of the tumor, either the distal esophagus or gastric cardia, and for prior radiation and/or chemotherapy. Computer-generated block randomization lists were prepared with block sizes of 4 and 6 in random order. Randomization by telephone was centrally performed at the Trial Office of the Department of Oncology, Erasmus MC Rotterdam. A written informed consent was obtained from all patients prior to enrollment. The study was approved by the Central Committee on Research Involving Human Subjects in The Netherlands.

Intervention

Stent placement was performed in two hospitals: the Erasmus MC Rotterdam (25 patients) and the Rijnstate Hospital Arnhem (5 patients). All stents were placed by endoscopists who were well acquainted with the characteristics of the stent used in this study, which was the FerX-Ella stent with or without anti-reflux valve (Figure 1). The FerX-Ella stent is supplied in a compressed form inside the introducer with an outer diameter of 20 Fr. The stent is composed of individual segments made of zigzag formed stainless steel wire. Both the zig- and the zag-ends of the wire form small loops. These loops fit into small stainless steel tubes connecting the individual segments. The stents are supplied in lengths of 90 mm, 120 mm or 150 mm, depending on the numbers of segments. The proximal segment has a purse string made of para-aramid thread. The ends of this thread are connected to each other by a golden tube that serves as a radiopaque marker. Traction on this thread reduces the diameter of the

stent cone. The stent inside the introducing sheath can be directed to a particular position in the esophagus or cardia and withdrawn from the sheath. The body of the

stent has a diameter of 20 mm, whereas the proximal cone has a diameter of 36 mm. The stent is covered with a polyethylene foil, which is applied to both the outside and inside of the stent. The outer foil layer is sealed to the inner layer, thus fixing the foil firmly to the wire skeleton. At the distal end of the stent, the polyethylene foil extends 47 mm beyond the lower metal cage to form a "windsock"-type valve (foil thickness 0.015 mm). The stent is supplied sterile and is designed for single use only. The material composition as well as the design of the FerX-Ella stent without anti-reflux valve is identical to the anti-reflux stent, however without the windsock-type valve.

Study endpoints and follow-up

The primary endpoint of the study was gastroesophageal reflux. Secondary endpoints were dysphagia score during follow-up, technical success of placement, complications, treatment for recurrent dysphagia, and survival.

Gastroesophageal reflux was assessed both by interviews and 24-hr pH monitoring. At 2 weeks after stent placement, all patients were asked to undergo 24-hour esophageal pH monitoring. After an overnight fast, a pH probe was inserted. The pH probe was connected to a digital portable recorder (Digitrapper MK III and pH probes, Synectics Medical, Stockholm, Sweden) and positioned 5 cm proximal to the gastroesophageal junction within the stent lumen. The position of the probe was verified by a chest X-ray (Figure 2). A reference electrode was attached to the upper chest. Patients were instructed to keep a diary recording meal times and the timing and type of reflux-like symptoms. Patients were encouraged to pursue their everyday activities and usual diets. At the beginning of the 24-h pH monitoring, the electrode and the system were calibrated for pH 4 and pH 7. Reflux was defined as pH of <4, and reflux time was defined as the interval until pH is >4. Analysis of the recorded data was performed using standard, commercially available computer software (Medical Measure Systems, Enschede, the Netherlands).

Experienced gastroesophageal reflux was assessed by the European Organization for Research and Treatment of Cancer (EORTC) OES-23[17], before treatment and at 14 days after treatment, and also by specific asking for reflux symptoms on regular follow-up interviews every 2 months until death. The EORTC OES-23 measure determines disease specific HRQoL which is relevant to patients with esophageal carcinoma. The indigestion scale of this measure is composed of 3 questions on heartburn. The total score was linearly transformed such that the scales ranged from 0 to 100 with a higher scale score representing a higher level of symptoms.

Dysphagia scores were graded as 0 = ability to eat a normal diet, 1 = ability to eat some solid food, 2 = ability to eat some semisolids only, 3 = ability to swallow liquids only, and 4 = complete dysphagia (18). Major complications were defined as life-threatening or causing severe distress, such as perforation, hemorrhage (hematemesis, melena, or a significant drop in hemoglobin level), fistula formation and severe pain, whereas minor complications were defined as not life-threatening or causing mild to moderate discomfort, such as mild pain and gastroesophageal reflux. Early complications were defined as complications occurring within 7 days after treatment. Complications occurring more than 7 days after stent placement were defined as late complications, although it was often unknown whether these were related to the stent or disease progression. Recurrent dysphagia was defined as the occurrence of tumor overgrowth, stent migration, or food bolus obstruction, all causing dysphagia.

All patients were evaluated before stent placement, 2 weeks after stent placement, 2 months after placement and then at a 2 months intervals until death. Regular follow-up was performed through telephone calls to the patient and/or the patient's primary care physician. If indicated, patients were readmitted for clinical evaluation. For patients who were still alive at the end of the study (October 30, 2003), follow-up was at least 6 months.

Statistics

Power calculations had shown that a sample size of 20 patients (10 in each group) was necessary to find a significant difference (α=0.05) in esophageal acid exposure time if this was 20% of the time in patients with a FerX-Ella stent with anti-reflux valve and 40% of the time in patients with an open FerX-Ella stent. Because a number of patients, for various reasons, did not undergo 24-hour esophageal pH monitoring, we continued the study until ten more patients were included (30 in total), but even then the statistical power was not achieved because of failure to perform 24-hr pH monitoring in all patients.

Results were expressed as means ± standard deviation (SD) or median scores with the 25^{th} and 75^{th} percentile. Differences in esophageal acid exposure time and dysphagia score improvement between the two types of stents were determined by the non-parametric Kruskall-Wallis test. Dysphagia scores and scores on the indigestion scale of the EORTC OES-23 (17) for each stent type on the day of stent placement and 14 days after treatment were compared with Wilcoxon's signed rank test. Complications and treatment for recurrent dysphagia for each of the two groups were compared using Kaplan-Meier and log rank tests to adjust for time of

occurrence and survival differences. Survival of the two groups was calculated and compared using Kaplan-Meier curves and log rank testing. A p value of <0.05 was considered as statistically significant.

RESULTS

Clinical characteristics

The two patient groups were similar in their clinical characteristics (Table 1). Prior to stent placement, 8 patients had been treated with chemotherapy, whereas none had received radiation therapy. Chemotherapy consisted of carboplatin and paclitaxel (n=5), cisplatin and paclitaxel (n=2), or 5-fluorouracil, cisplatin and leucovorin (n=1).

Table 1: Clinical characteristics of 30 patients given a FerX-Ella stent with or without anti-reflux valve for palliation of dysphagia due to carcinoma of the distal esophagus or gastroesophageal junction.

	FerX Ella stent with anti-reflux valve (N=15)	**FerX Ella stent without anti-reflux valve (N=15)**
Age (yr)	68 ± 8	69 ± 11
Gender (M/F)	12/3	12/3
Mean tumor length (cm)	8.3 ± 3.1	7.1 ± 2.5
Tumor histology (no. of patients)		
Squamous cell carcinoma	3 (20%)	3 (20%)
Adenocarcinoma	12 (80%)	12 (80%)
Reason for palliative treatment		
Metastases	12 (80%)	11 (73%)
Poor medical condition	3 (20%)	2 (13%)
Combination	-	2 (13%)
Location of tumor (no. of patients)		
Distal esophagus	12 (80%)	12 (80%)
Cardia	3 (20%)	3 (20%)
Prior chemotherapy (no. of patients)	5 (33%)	3 (20%)

Outcome and survival

Successful placement of a FerX-Ella stent was achieved in 27 out of 30 patients (Table 2). In two patients (one in each treatment group), the stent migrated directly after placement. In another patient, the distal tip of the introduction set could not be removed due to the angled position of the stent at the gastroesophageal junction. The introduction system with the stent still mounted was removed and an Ultraflex stent was placed. In one patient, a second stent was needed because the initial stent partially migrated during the procedure leading to insufficient bridging of the stricture. Dilation to 9 mm prior to stenting was necessary in 4 patients (two in each treatment group).

Table 2: Outcome and survival in 30 patients given a FerX-Ella stent with or without anti-reflux valve for palliation of dysphagia due to carcinoma of the distal esophagus or gastroesophageal junction.

	Fer-X Ella stent with anti-reflux valve (N=15)	**Fer-X Ella stent without anti-reflux valve (N=15)**
Technical success (no. of patients)		
Single stent	13	13
Two stents	-	1
Total	13 (87%)	14 (93%)
Median dysphagia score (25-75 percentile) Day 0 → day 14*	3 (3-3) → 1 (0-2)	3 (3-4) → 0 (0-2.5)
Indigestion scale score EORTC OES-23 (median (25-75 percentile) on a 100 point scale, 0=best) Day 0 → day 14†	22 (11-33) → 22 (11-44)	11 (0-33) → 11 (11-28)
Median survival (days) (95% CI)	107 (11-203)	87 (58-116)
Cause of death (no. of patients)		
Tumor progression	11	11
Not related to tumor	1	3
Alive	3	1

* p=NS; improvement within each treatment group: anti-reflux: p=0.002, open stent: p=0.005
†p=NS

Median dysphagia score improved from 3 before treatment to 1 two weeks after treatment in patients with an anti-reflux stent and from 3 to 0 in patients with an open stent. Both the degree of improvement of dysphagia and median survival were not different between the two patient groups. The majority of patients (22/30) died from tumor progression and 4 patients died from causes unrelated to either the tumor or stent placement. There were no stent-related deaths. After a follow-up of at least 6 months, 4 patients were still alive.

24-hour pH monitoring and reflux symptoms

Twenty-four hour pH monitoring was performed in 12 of the 30 patients (9 patients with an anti-reflux valve and 3 patients with an open stent). One measurement in a patient with an open stent was excluded because the patient had used a proton-pump inhibitor. Reasons for not undergoing pH monitoring in the other 18 patients were: placement of another stent type (n=4), a poor medical condition (n=4), patient deceased (n=3), patient refusal (n=5), stent migration (n=1), and technical problems in positioning the pH probe (n=1).

Increased esophageal reflux exposure (normal < 4%) was found in 6/9 patients with an anti-reflux stent and in 1/2 patients with an open stent. The median total reflux times were 23% in the anti-reflux stent group (range: 0-65%, n=9) and 10% in the open stent group (values: 0.1% and 19%, Figure 3, p=NS). The median number of reflux episodes longer than 5 minutes was 14 (25-75 percentile: 2-19) in the anti-reflux stent group and 5 (values: 0 and 10) in the open stent group (normal: <1) (p=NS).

Reflux symptoms were reported by 3/12 (25%) patients with an anti-reflux stent and by 2/14 (14%) patients with an open stent (Table 3). Of the 7 patients with abnormal esophageal acid exposure time as measured by 24-hour pH monitoring, 2 patients (one in each treatment group) reported reflux symptoms. Median scores of the indigestion scale of the EORTC OES-23 were not different between both groups on the day of treatment and at 14 days after stent placement (Table 2). One symptomatic patient with an anti-reflux stent underwent an endoscopy, which showed reflux-esophagitis grade C according to the Los Angeles classification. All symptomatic and asymptomatic patients with abnormal pH recordings were treated with a proton-pump inhibitor.

Figure 1: The FerX-Ella stent with and without anti-reflux valve.

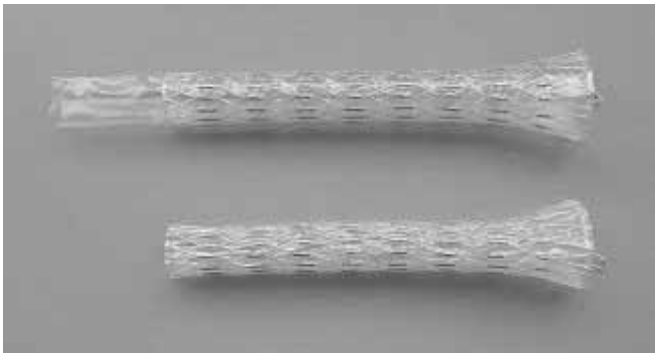

Figure 2: Chest X-ray of the FerX-Ella stent with anti-reflux valve after positioning of the pH probe for the 24 h pH monitoring. The arrow shows the end of the pH-probe in the lumen of the stent (positioned 5 cm proximal to the gastroesophageal junction).

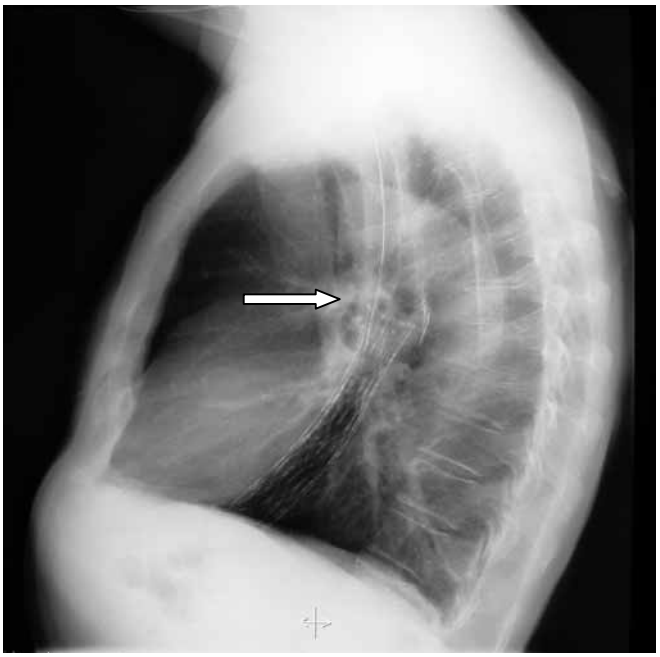

Figure 3: Total reflux time after 24 h pH-monitoring in patients with a FerX-Ella stent with anti-reflux valve (n=9) or an open FerX-Ella stent (n=2) for palliation of dysphagia due to carcinoma of the distal esophagus or gastroesophageal junction.

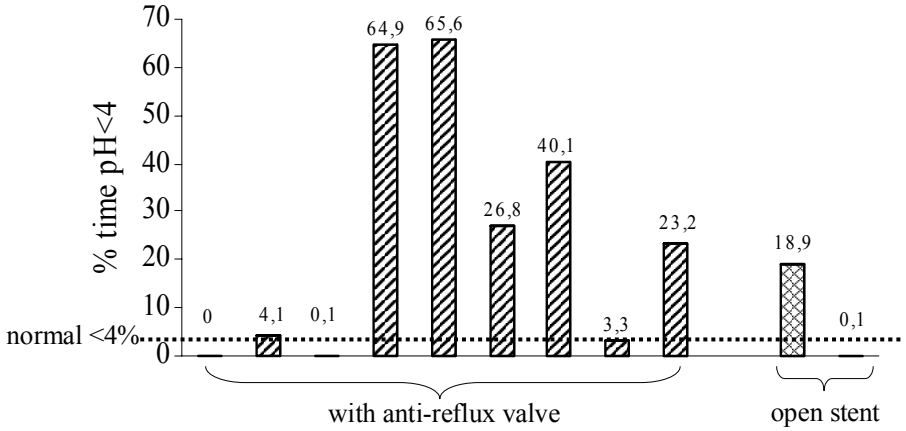

Figure 4: Endoscopic view from inside the stent showing the inverted membrane of the anti-reflux valve, causing complete obstruction of the stent.

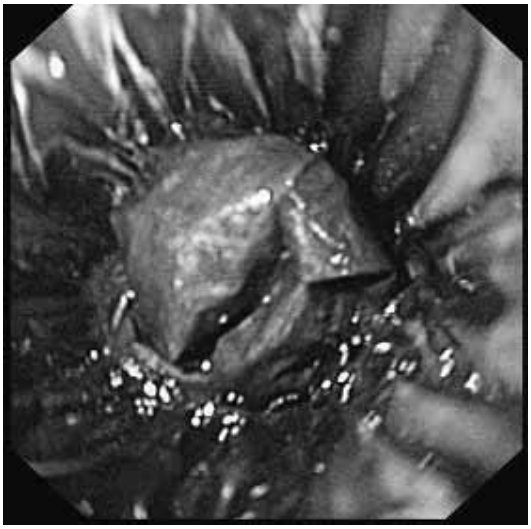

Table 3: Complications and persistent/recurrent dysphagia in 30 patients given a FerX-Ella stent with or without anti-reflux valve for palliation of dysphagia due to carcinoma of the distal esophagus or gastroesophageal junction

	Fer-X Ella stent with anti-reflux valve (N=15)	Fer-X Ella stent without anti-reflux valve (N=15)
Total complications	7 (47%)	5 (33%)
Major complications	3 (20%)	3 (20%)
≤ 7 days		
Severe pain	1	1
> 7 days		
Hemorrhage	2	1
(Aspiration) pneumonia	-	1
Minor complications	4 (27%)	2 (13%)
Mild retrosternal pain	1	-
Gastroesophageal reflux	3	2
Recurrent dysphagia	6 (40%)	2 (13%)
Stent migration	5	2
Inwards folded anti-reflux valve	1	-

Complications and recurrent dysphagia

There were no differences in the occurrence of major complications between patients with or without an anti-reflux stent (3/15 (20%) vs. 3/15 (20%) (Table 3). Two patients (one in each treatment group) experienced severe pain after stent placement and needed high doses of narcotic analgesics. Late major complications consisted predominantly of hemorrhage (n=3), for which one patient underwent endoscopy showing that the hemorrhage was caused by bleeding from the tumor. None of these 3 patients died from bleeding. One patient with an open stent developed (aspiration) pneumonia 3 weeks after stent placement. This patient had not undergone 24-hour pH monitoring.

There was no difference in the number of patients treated for recurrent dysphagia between the two treatment groups (Table 3). Recurrent dysphagia after stent placement was predominantly caused by stent migration in 7 (23%) patients, 5 of which occurred in the anti-reflux stent group (p=NS). Migration occurred in the anti-reflux group on the day of treatment in one patient and at 7, 21, 120 and 288 days after treatment, in the open stent group at 11 and 77 days after treatment, and was

treated by placement of a second stent (n=5), or repositioning of the stent (n=2). In one patient, the foil of the anti-reflux valve had inverted into the distal part of the stent, causing complete obstruction (Figure 4). During endoscopy, the foil was pushed back into the stomach, effectively relieving the obstruction.

DISCUSSION

This is the first randomized study evaluating the ability of a stent with an anti-reflux mechanism, i.e., the FerX-Ella stent, to prevent gastroesophageal reflux in patients with inoperable cancer of the distal esophagus and gastric cardia and comparing it with a control group that was treated with a standard open stent of the same design. The function of the anti-reflux valve was not only assessed by patient interviews, but also by 24-hour pH monitoring in 11/30 (37%) patients. There were no significant differences in improvement of dysphagia, the occurrence of complications and recurrent dysphagia, or survival between both stent types, however the anti-reflux valve of the FerX-Ella stent failed to prevent the occurrence of gastroesophageal reflux.

Dua et al. (15) reported placing a Z-stent with a similar windsock-type anti-reflux mechanism, or an open Z-stent, in the distal esophagus of 5 dogs and performed ambulatory pH monitoring. They demonstrated that the mean esophageal acid exposure time decreased from 49% with an open stent to 1% with an anti-reflux stent. Subsequently, they found that 11 patients treated with this anti-reflux stent had daytime heartburn and regurgitation scores less than 1 (score 10 = severe) and no nocturnal reflux symptoms. In another study, Laasch et al.(16) reported that only 3/25 (12%) patients treated with an anti-reflux Z-stent had symptoms of gastroesophageal reflux against 24/25 (96%) patients treated with a Flamingo Wallstent, a different stent design without anti-reflux valve. Both studies concluded that the anti-reflux Z-stent was effective in reducing symptoms of gastroesophageal reflux (15, 16). Finally, Köcher et al. (12) placed a FerX-Ella stent with anti-reflux valve in 18 patients with cancer at the gastroesophageal junction and reported only minor heartburn in two patients and no significant gastroesophageal reflux on barium swallow studies.

How can the different outcomes of the present study and those of the other studies be explained? In the first place, our study highlights the importance of assessing the function of anti-reflux stents not only by patient interviews, but specifically by performing 24-hour pH recordings within the stent lumen (Figure 2). Although only 3/12 (25%) patients with an anti-reflux FerX-Ella stent reported symptoms of

gastroesophageal reflux (Table 3), 6/9 (66%) patients with the anti-reflux stent were found to have gastroesophageal reflux as measured by pH monitoring (Figure 3).
Symptoms of gastroesophageal reflux with standard open stents have been reported in 5-15% of patients in other studies (11, 19, 20). In the present study and in spite of repeated interviews, again only 2/14 (14%) patients with an open FerX-Ella stent reported symptoms of gastroesophageal reflux. Therefore, it is likely that in the majority of these patients with a short life expectancy, gastroesophageal reflux is asymptomatic. This low prevalence of symptomatic reflux may partly be explained by the fact that patients with Barrett's esophagus, who form the majority of the patients with distal (adeno)carcinomas, have a decreased esophageal chemoreceptor sensibility (21-23). In addition, tumor infiltration of the vagus nerve may reduce acid production. As there have only been very rare reports of severe esophagitis after stent placement (24), which responds well to treatment with a proton-pump inhibitor, the question arises whether the considerable technical and financial efforts directed towards developing anti-reflux stents are justified.
Another important explanation for the discrepancies in outcome between our study and that of the other studies could be the different valve design of the anti-reflux FerX-Ella stent and the anti-reflux Z-stent. The general principle of this anti-reflux valve is that the membrane cover of the stent extends beyond the lower metal cage to form a "windsock"-type valve (Figure 1). While allowing food to pass into the stomach, this mechanism should prevent the occurrence of gastroesophageal reflux by the empty windsock being compressed by the intra-abdominal pressure and thus closing off its lumen. Since it is important that patients retain their ability to belch or vomit and to prevent gas bloating after meals, the anti-reflux valve of the Z-stent can invert itself into the stent lumen under an intra-abdominal and an intra-thoracic pressure gradient of around 35 mm Hg (15). An inversion pressure at this level would seem to be adequate in preventing reflux during normal activities and sleep.
The valve membrane of the FerX-Ella stent differs from the Z-stent by the material used for the membrane (FerX-Ella stent: polyethylene vs. Z-stent: polyurethane), the length (FerX-Ella stent: 47 mm vs. Z-stent: 80 mm) and thickness of the membrane (FerX-Ella stent: 0.015 mm vs. Z-stent: 0.017 mm). Dua et al. (15) have shown that reducing the thickness of the membrane of the Z-stent from 0.017 mm to 0.015 mm decreases the pressure necessary to invert the valve membrane into the stent by one-third. Moreover, polyethylene is a less rigid material than polyurethane. We therefore suspect that these different stent characteristics of the FerX-Ella stent may well explain its failure to prevent gastroesophageal reflux.

Although the diameter of the valve lumen is the same as the shaft lumen of the Fer-X Ella stent, we found no evidence of the valve interfering with the passage of food (median improvement in dysphagia score from 3 to 1 in both the anti-reflux and open stent group). When the valve membrane inverts during belching or vomiting, it should be possible to revert it to its anti-reflux position by drinking some water. We instructed all patients to do so after events which could potentially raise the intra-abdominal pressure or in case of symptoms of gastroesophageal reflux. The membrane of the anti-reflux valve inverted into the distal part of the stent in one patient, which caused complete obstruction of the stent (Figure 4). Drinking of water failed to revert the valve into its anti-reflux position. At endoscopy, the membrane was carefully pushed back into the stomach, relieving the obstruction.

It is known that stent migration is more likely to occur when stents are placed across the gastroesophageal junction, because in this position the distal part of the stent projects freely into the fundus of the stomach and this part cannot fix itself to the wall (9). The Fer-X Ella stent was no exception, in fact with 7/30 episodes of migration its performance was rather poor. The trend towards more episodes of stent migration with the anti-reflux stents than with the open stents (5 (33%) vs. 2 (13%); p=NS) was not anticipated because the anti-reflux valve is predominantly positioned in the upper part of the stomach away from strong peristaltic contractions in the gastric antrum. In addition, the FerX-Ella stent has a proximal diameter of 36 mm to prevent migration. However, our results would suggest that the FerX-Ella stent needs additional measures to prevent the stent from migrating, for example an uncovered proximal segment to allow the normal mucosa above the tumor to project into the stent lumen or metal barbs on the outside of the stent to anchor it into the tumor.

In conclusion, the FerX-Ella stent provides symptomatic relief of malignant dysphagia, however its anti-reflux valve fails to prevent gastroesophageal reflux. In addition, stent migration, particularly with anti-reflux stents, was seen in almost one-quarter of patients. Changes in the design of the stent and its anti-reflux valve are needed to improve its clinical usefulness. In addition, we believe that the efficacy of all anti-reflux stents should be evaluated by 24-hour pH monitoring, although our study illustrates the practical difficulties in achieving such measurements. Finally, companies planning to introduce new stent designs with anti-reflux mechanism on the market would do well to wait with marketing until randomized trials have provided solid data for both their efficacy and their necessity.

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8

General Discussion

In this thesis the first randomized study between the two most widely used methods for the palliation of dysphagia from esophageal cancer, i.e., single dose brachytherapy and metal stent placement, is reported. Apart from relief of dysphagia and complications as outcome measures an extended quality of life study and a cost study were performed. In addition, specific brachytherapy- and stent-related problems were investigated. Using this data, a more evidence-based treatment advice can probably be given to patients needing palliation of dysphagia from esophageal cancer.

Main conclusions from this thesis:

- Dysphagia improved more rapidly after stent placement than after brachytherapy, but brachytherapy resulted in a better relief of dysphagia in the long term.
- Stent placement was associated with more complications compared to brachytherapy which was mainly due to a higher incidence of hematemesis after stent placement.
- More than 40% of the patients needed additional treatment for persistent or recurrent dysphagia after stent placement or brachytherapy with no difference between both treatments.
- Brachytherapy gave better overall scores on health-related quality of life (HRQoL) scales compared to stent placement. Most items of the generic HRQoL scales deteriorated during follow-up in both treatment groups, however, the decline was more pronounced in the stent group. On the disease-specific HRQoL scales, major improvements were seen on the dysphagia and eating scales, whereas the other scales remained almost stable during follow-up. This suggests that the disease-specific scales are less sensitive in measuring HRQoL than the generic scales in this group of patients.
- In spite of the higher initial costs for stent placement than for brachytherapy total medical costs were similar. Cost considerations should therefore not play an important role in decision making on the most appropriate palliative treatment strategy for patients with dysphagia from esophageal cancer.

In general, single dose brachytherapy is preferable to metal stent placement as the initial treatment for the palliation of dysphagia from esophageal cancer. Our results suggest that stent placement should be reserved for patients with severe dysphagia in combination with a short life expectancy, who need a rapid relief of dysphagia.

Another group in which stent placement should be considered are patients with persistent or recurrent tumor growth after single dose brachytherapy.

Secondary conclusions:

- There is a wide variation in the use of diagnostic procedures and treatment strategies for patients with esophageal cancer in the Netherlands. This stresses the need for a more evidence-based and uniform approach to both diagnostic procedures and treatment for this malignancy.
- Patients with stenotic tumors that cannot be passed endoscopically or who previously underwent chemotherapy are poor candidates for single dose brachytherapy. For these patients alternative palliative treatment modalities should be considered.
- Patients with dysphagia from inoperable esophageal cancer who previously underwent radiation and/or chemotherapy can effectively and safely be treated with stent placement.
- Re-interventions for stent-related recurrent dysphagia are effective in over 90% of patients and these improve dysphagia. An effective treatment strategy for both tumor overgrowth and stent migration is placement of a second stent, or, in some cases of migration, repositioning of the stent. Patients with recurrent dysphagia after palliative treatment should therefore be referred for endoscopy as this problem is almost always amenable to treatment.
- The new design stent for the prevention of gastro-esophageal reflux, the FerX-Ella stent with anti-reflux valve, failed to prevent gastro-esophageal reflux. In addition, in a relatively high number of patients the stent migrated. Changes in the design of the stent and its anti-reflux valve are needed to improve its clinical usefulness.

PERSPECTIVES AND FUTURE RESEARCH

Single dose brachytherapy

In this thesis, we describe the results of our retrospective study of single dose brachytherapy in 149 patients with dysphagia from inoperable esophageal cancer and the randomized trial comparing single dose brachytherapy versus metal stent placement. The occurrence of complications, recurrent dysphagia and survival of patients were similar in both studies. However, the relief of dysphagia was lower in the retrospective study. This can partly be explained by incomplete patient data in

our retrospective study but also by the intensive follow-up in our comparative trial. Patients with no improvement in dysphagia scores within a few weeks after treatment received an additional treatment mostly consisting of stent placement. This intensive follow-up probably leads to improved outcome data of palliative treatment strategies.

Almost half of the patients needed an additional intervention for persistent or recurrent dysphagia after single dose brachytherapy. One way to improve the results of brachytherapy is to improve the selection of patients that are eligible for this treatment. This was described in chapter 5B. It is uncertain whether a single treatment of 12 Gy brachytherapy was the optimal dose for this treatment. The biological effects of brachytherapy might be improved by increasing and/or fractioning the delivered dose. Different doses of brachytherapy were compared in 172 patients with advanced esophageal (mainly squamous cell) carcinoma in a study from South Africa (1). Patients were randomized to 12 Gy in 2 sessions, 16 Gy in 2 sessions or 18 Gy in 3 sessions. Patients who received 16 Gy or 18 Gy in two sessions did significantly better than patients who received 12 Gy in 2 sessions in terms of dysphagia-free survival and persistent tumor growth in the esophagus after treatment. The treatment regimes with 16 Gy in 2 sessions and 18 Gy in 3 sessions were again compared in a randomized trial with 232 patients with similar results for the two treatment regimes (2). Therefore, additional studies are needed to investigate whether a higher and/or fractionated dose of brachytherapy will increase the efficacy of dysphagia relief in patients with metastatic disease and/or a poor general condition.

Metal stent placement

New stent designs have recently been developed or are still under development to prevent stent-related problems and improve palliation of esophageal cancer. In order to prevent the high fraction of recurrent dysphagia after stent placement improved stent designs need to be developed which prevent both tumor overgrowth and stent migration. Currently, a new type of stent is under investigation in the Erasmus MC, the Niti-S stent, with a double layer consisting of a covered inner layer and an uncovered outer layer. This design should reduce, if not eliminate, the occurrence of stent migration. Other available new stent designs which claim to reduce the occurrence of recurrent dysphagia, for example the self-expanding plastic Polyflex stent (3), should to be compared in a randomized study.

In this thesis we describe the results of the FerX-Ella stent designed to prevent gastro-esophageal reflux if stents are placed across the gastro-esophageal junction. The FerX-Ella stent provided symptomatic relief of dysphagia, however its anti-reflux valve failed to prevent gastro-esophageal reflux. We believe that the efficacy of anti-reflux stents should be evaluated by 24-hour pH monitoring, although our study illustrates the practical difficulties in achieving such measurements. Companies planning to introduce new stent designs with anti-reflux mechanism to the market would do well to wait with marketing until randomized trials have provided solid data for both their efficacy and their necessity.

Future new types of stents, which are currently being developed, include biodegradable stents, stents with a radioactive coating and drug-eluting stents. Biodegradable stents have been developed for benign stenoses (4, 5), however a possible application could be the initial treatment of dysphagia in patients undergoing palliative chemotherapy or patients with severe dysphagia undergoing neo-adjuvant chemotherapy. Since treatment results of chemotherapy for esophageal carcinoma have improved over the last few years (6, 7), an increased proportion of patients with this malignancy will likely be considered for treatment with chemotherapy.

The incorporation of beta-emitting agents and cytotoxic agents in esophageal stents may increase the efficacy of stents, particularly in the prevention of (recurrent) tumor overgrowth at both ends of the stent. Clinical experience has been obtained with radio-active stents and drug-eluting stents in coronary arteries of humans. For the esophagus, only experience with animal models is available. In healthy dogs the radioactive stent caused some fibrosis with radiation damage to the normal esophagus but no serious complications such as perforation or fistula formation occurred (8). The safety and efficacy of radio-active and drug-eluting stents in malignant strictures in the esophagus need further evaluation in clinical trials.

Single dose brachytherapy versus metal stent placement

Study design

We preformed a randomized study in nine hospitals in the Netherlands comparing single dose brachytherapy versus metal stent placement for the palliation of dysphagia from esophageal cancer. Participating centers included 3 university centers and 6 general hospitals. In this way we were able to recruit more than 200

patients within 2.5 years, which is remarkable considering the relatively low incidence of esophageal carcinoma in the Netherlands. Patients were well-informed on the aim and design of the study before being randomized and only 44 (17%) of the 253 eligible patients refused to participate. The most common reason for refusal was the fact that the majority of these patients had a specific preference for one of the two treatment modalities. In all participating centers a gastroenterology and a radiotherapy department were present and the physicians from these departments had extended clinical experience with both stent placement and brachytherapy. Before the start of the study several meetings were organized to discuss the design and logistics of the trial, in order to enhance uniform treatment strategies in each center. During the study the study coordinators of the participating centers had contact on a regular basis.

Many patients needed additional treatments after both single dose brachytherapy and stent placement. Since a specific evidence-based protocol for these re-interventions had not been developed the choice of treatment was made by the responsible physician. Placement of a second stent was the most frequently used treatment for recurrent dysphagia after initial stent placement. In case of persistent or recurrent dysphagia after brachytherapy placement of a stent was also the most widely used treatment modality. By doing so these patients received, in addition to brachytherapy, the treatment modality of the other randomization arm. Due to the intention-to-treat set-up of the study and its analyses, all complications and costs of the non-assigned treatment were accounted to the randomized treatment group. In our recommendations for the palliative treatment of dysphagia from esophageal cancer we conclude that single dose brachytherapy is preferable as the *initial* treatment. However, stent placement might well be used for persistent or recurrent dysphagia after single dose brachytherapy.

Follow-up

An important problem with multicenter trials is to obtain complete follow-up data. In this study patients were followed by home visits from a specialized research nurse at 14 days, 1 month and then monthly until one year after treatment. After one year of follow-up patients were visited every 3 months and/or telephone calls to the patient and the patients' practitioner were made. The specialized nurse collected outcome data on dysphagia, complications, additional treatments, quality of life and costs (hospital costs, interventions and extramural care). In this way we obtained

complete follow-up data (in more than 95% of patients) which resulted in a unique database.

An unexpected result of this study was the enormous success of these home visits by specialized research nurses. The research nurses were specifically trained to support patients with incurable esophageal carcinoma. These nurses assisted patients with filling out the large number of questionnaires and checklists for the quality of life study and the cost study. However, the nurses were even more important in giving advice and support to this patient group with a poor survival. Whether home visits by specialized nurses could be an alternative to regular control visits to the clinic for patients who have undergone treatment for esophageal cancer is currently under investigation in a randomized study. Acceptability, quality of life and costs are the main outcome measures of this study.

In our study health related quality of life (HRQoL) was investigated with a variety of validated measures. Disease specific quality of life was assessed with the dysphagia score (9), the esophageal specific European Organization for Research and Treatment of Cancer (EORTC) OES-23 measure (10) and a visual analogue pain scale. Generic HRQoL was assessed with the oncology-specific EORTC QLQ-C30 measure (11) and the EQ-5D including an index score and visual analogue scale (EQ-VAS) for self-rated health (12). Single dose brachytherapy gave better overall scores on HRQoL scales compared to stent placement for the palliation of esophageal cancer. In our opinion studies comparing different treatment modalities for esophageal carcinoma should also incorporate quality of life questionnaires to determine, apart from technical aspects, whether these treatments are of benefit from the point of view of patients.

Palliation of dysphagia from esophageal carcinoma

Recently, the guideline 'Esophageal carcinoma' of the Comprehensive Cancer Center (2003) has become available, whereas the evidence-based guideline on the diagnosis and treatment of esophageal cancer under the flag of the Dutch institute for Healthcare CBO will soon become available (fall 2004). These guidelines need to be evaluated in daily practice if they will result in a more uniform and effective strategy for the treatment of esophageal cancer. New treatment results should be incorporated in regular updates of these guidelines. In addition, it is important that implementation programs for these guidelines will be developed.

From this thesis we can conclude that the current recommendation for the palliative treatment of dysphagia from esophageal cancer would be single dose brachytherapy as the initial treatment. Stent placement should be reserved for patients with severe dysphagia in combination with a short life expectancy, needing a rapid relief of dysphagia and for patients with persistent or recurrent tumor growth after single dose brachytherapy.

However, the presently available treatment modalities for palliation of dysphagia from esophageal cancer are, as yet, not optimal in achieving fast and sustained dysphagia relief with minimal morbidity and mortality. Metal stent are reasonably effective in improving dysphagia, however, both the complication rate and the number of re-interventions necessary for recurrent dysphagia are still too high. Single dose brachytherapy is a more effective and safer alternative than stent placement, although both tumor persistence and tumor recurrence have a negative impact on the short- and long-term effect of palliation of dysphagia. It remains to be studied whether results of brachytherapy or stent placement can be improved by higher and/or fractionated radiation doses or by improved stent designs without jeopardizing safety.

Randomized controlled trials comparable to the trial described in this thesis are ideally needed to compare (new) palliative treatment modalities with special reference to dysphagia relief, complications, interventions for recurrent dysphagia, quality of life after treatment and costs. In addition, improvements in the selection of patients for a particular palliative treatment modality will make a more individualized palliative treatment strategy possible. In this way a more optimal palliative treatment strategy for esophageal cancer will be achieved.

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Summary

The prognosis of esophageal cancer is poor with a 5-year survival of 10-15%. In addition, over 50% of patients with esophageal cancer already have an inoperable disease at presentation. The majority of these patients require palliative treatment to relieve progressive dysphagia. Metal stent placement and single dose brachytherapy (intraluminal radiation) are the two most widely used palliative treatments for dysphagia from esophageal cancer, however, their relative merits are unknown (**Chapter 2**).

In this thesis, we present the results of the first randomized trial comparing metal stent placement with single dose brachytherapy for the palliation of dysphagia from inoperable esophageal cancer. Between December 1999 and June 2002, 209 patients with dysphagia from inoperable carcinoma of the esophagus or gastro-esophageal junction were randomized to placement of a metal stent (n=108) or single dose brachytherapy (n=101). Patients randomized to stent placement received an Ultraflex stent, patients in the brachytherapy group were treated with a single intraluminal radiation dose of 12 Gray. We compared the two treatments with respect to relief of dysphagia, complications, treatment for persistent or recurrent dysphagia, health related quality of life and costs. Participating centers included 3 university and 6 general hospitals in the Netherlands. Patients were followed by monthly home visits from a specialized nurse who collected outcome data using standardized questionnaires. If indicated, patients were readmitted for clinical evaluation and re-treatment (**Chapter 6**).

Dysphagia improvement was more rapid after stent placement than after brachytherapy, but long term relief of dysphagia was better after brachytherapy. Complications occurred more often after stent placement (33% vs. 21%), which was mainly due to a higher incidence of late hemorrhage (13% vs. 5%). The number of patients treated for persistent or recurrent dysphagia was similar for both treatment groups (40% vs. 43%), as was median survival (**Chapter 6A**).

We obtained longitudinal data on disease specific and generic health-related quality of life. Disease specific quality of life was assessed with the dysphagia score, the esophageal cancer specific EORTC OES-23 measure and a visual analogue pain scale. Generic HRQoL was assessed using the oncology-specific EORTC QLQ-C30 measure and the EQ-5D including an index score and a visual analogue scale (EQ-VAS) for self-rated health. Treatment with single dose brachytherapy gave better overall scores on HRQoL scales compared to stent placement. Major improvements

were seen on the dysphagia and eating scales of the disease specific EORTC OES-23 after treatment, however most items of the different HRQoL scales deteriorated during follow-up. Generic HRQoL scales were more responsive in measuring patients' functioning and well-being during follow-up than disease specific HRQoL scales **(Chapter 6B)**.

The initial costs of stent placement were higher than the costs of brachytherapy (€1,500 vs. €570). However, total medical costs were similar (stent €11,195 vs. brachytherapy €10,078). Total hospital stay during follow-up was 11.5 days after stent placement versus 12.4 days after brachytherapy, which was responsible for the high intramural costs in both treatment groups (stent: €6,512 vs. brachytherapy: €7,982). Therefore, cost considerations should not play an important role in decision making on the appropriate palliative treatment strategy for patients with dysphagia from esophageal cancer (**Chapter 6C**).

Brachytherapy resulted in a better relief of dysphagia during follow-up and was associated with fewer complications. In addition, there was a benefit in quality of life after brachytherapy. The number of repeated procedures for persistent or recurrent dysphagia and costs of both treatment modalities were similar.
Based on this randomized study single dose brachytherapy is preferable to stent placement as the initial palliative treatment for patients with dysphagia from esophageal cancer. Stent placement may be reserved for patients with severe dysphagia in combination with a short life expectancy and for persistent or recurrent tumor growth after brachytherapy (**Chapter 6**).

In order to investigate the currently used diagnostic procedures and treatment strategies for esophageal cancer we sent a questionnaire to all Dutch clinicians (internists, gastroenterologists and surgeons) working in the field of gastroenterology. Almost 90% of the clinicians treated fewer than 20 patients annually, mostly in their own hospital. Computer tomography was the most frequently used staging procedure. Endoscopic ultrasound was less frequently used. The treatment choice for the presented patient vignettes varied widely among clinicians. Factors influencing the choice to operate or not were metastases, loco-regional tumor ingrowth, poor general health and advanced age. Stent placement was the most frequently chosen method for the palliation of dysphagia from esophageal cancer. This survey indicates that at present there are wide variations in the strategies for diagnosis, staging and treatment of patients with esophageal

cancer. There is a need for more evidence-based and uniform approach to both diagnostic procedures and treatment for this malignancy (**Chapter 3**).

Prior to our randomized trial between brachytherapy and stent placement, we performed a retrospective analysis over a 10-year period of 149 patients treated with brachytherapy in our center. Brachytherapy was administered in one (87%) or two (13%) sessions, at a median dose of 15 Gy. Dysphagia scores had improved from a median of 3 (liquids only) to 2 (semisolids), however dysphagia had not improved in 51 (49%) patients. Procedure related complications occurred in 7 (5%) patients. Late complications including fistula formation or bleeding occurred in 11 (7%) patients. Twelve (8%) patients experienced minor retrosternal pain. Median survival of the patients was 160 days. During follow-up, 55 (37%) patients experienced recurrent dysphagia. In 34 (23%) patients a metal stent was placed to relief persistent or recurrent dysphagia. From this retrospective trial we concluded that brachytherapy was a moderately effective treatment for the palliation of malignant dysphagia. The incidence of complications was low, however, persistent and recurrent dysphagia occurred frequently which often required additional treatment (**Chapter 4A**).

From our comparative study and the retrospective study we concluded that a disadvantage of single dose brachytherapy was the fact that almost half of the patients needed additional treatment for persistent or recurrent tumor growth after single dose brachytherapy. We investigated which baseline patient and tumor characteristics within our study influenced the occurrence of persistent and recurrent tumor growth after single dose brachytherapy. We found that dilation prior to treatment was a risk factor for persistent and recurrent tumor growth after single dose brachytherapy. In addition, there was a trend towards a higher risk for persistent tumor growth in patients previously treated with chemotherapy. For these patient alternative palliative treatment modalities should be considered (**Chapter 4B**).

In order to improve the palliation of esophageal cancer with metal stents we investigated several stent-related problems. An important issue of debate was whether prior radiation and/or chemotherapy (RTCT) increases the risk of complications after metal stent placement in patients with inoperable esophagogastric carcinoma. We therefore evaluated the influence of prior RTCT on the outcome of stent placement in 200 prospectively followed patients. Forty-nine of

these patients had received prior RTCT (chemotherapy n=35, radiation therapy n=8, or both n=6). The incidence of major complications, recurrent dysphagia and survival were not affected by prior RTCT, however retrosternal pain occurred more frequently in patients who had previously undergone RTCT. Therefore, placement of a metal stent is as safe and effective in patients with prior RTCT as in those without such treatment. (**Chapter 5A**).

Recurrent dysphagia after stent placement is also a frequently occurring problem. We investigated the causes of stent-related recurrent dysphagia, the time interval of occurrence after first stent placement, the procedures used for re-intervention and their outcomes. Two-hundred sixteen patients underwent placement of a metal stent (Ultraflex, n=75; Flamingo Wallstent, n=71; Z-stent, n=70) for palliation of dysphagia from esophageal cancer in our center and were followed prospectively. Recurrent dysphagia occurred in almost one-third of patients after stent placement. This was mainly caused by tumor overgrowth at the proximal and/or distal end of the stent, stent migration, and food bolus obstruction. Re-interventions for stent-related recurrent dysphagia were effective and improved dysphagia scores. The most effective treatment strategy for both tumor overgrowth and stent migration was placement of a second stent or, in cases of migration, stent repositioning. Patients with recurrent dysphagia should therefore be referred for endoscopy as this problem is almost always amenable to treatment (**Chapter 5B**).

New stent designs have been developed and are still under development to prevent stent-related problems and improve palliation of esophageal cancer. Metal stents deployed across the gastro-esophageal junction predispose to gastro-esophageal reflux. We assessed the efficacy of the FerX-Ella stent with an anti-reflux mechanism in preventing gastro-esophageal reflux. Patients with carcinoma of the distal esophagus or gastric cardia were randomized to receive either a FerX-Ella stent with a windsock-type anti-reflux valve (n=15) or a standard open FerX-Ella stent (n=15). We found that the FerX-Ella stent provided symptomatic relief against malignant dysphagia, however its anti-reflux valve failed to prevent gastro-esophageal reflux. Changes in the design of the stent and its anti-reflux valve are needed to improve its clinical usefulness (**Chapter 7**).

It remains to be studied whether results of brachytherapy or stent placement can be improved by higher and/or fractionated radiation doses or by improved stent designs without jeopardizing safety (**Chapter 8**).

Samenvatting

De prognose van slokdarmkanker is slecht met een 5-jaars overleving van zo'n 10-15%. Dit komt mede doordat meer dan de helft van de mensen met slokdarmkanker niet in aanmerking komt voor een operatie, m.n. ten gevolge van aanwezige metastasen of een slechte algemene conditie. Deze groep patiënten heeft vrijwel altijd een palliatieve behandeling nodig om voedselpassageklachten te verbeteren. De twee meest gebruikte methoden voor de palliatie van passageklachten ten gevolge van slokdarmkanker zijn het plaatsen van een zelf-ontplooibare stent (stent) of het verrichten van een inwendige bestraling (brachytherapie) in de slokdarm. Deze twee behandeling zijn nog niet eerder met elkaar vergeleken (**hoofdstuk 2**).

In dit proefschrift worden de resultaten beschreven van het eerste gerandomiseerde onderzoek waarin stentplaatsing met brachytherapie wordt vergeleken voor de palliatie van passageklachten ten gevolge van slokdarmkanker. Tussen december 1999 en juni 2002 werden 209 patiënten met passageklachten op basis van een inoperabel slokdarmcarcinoom ten gevolge van metastasen of een slechte algemene conditie gerandomiseerd voor stentplaatsing (n=108) of brachytherapie (n=101). In de stentgroep werd een Ultraflex stent geplaatst en in de brachytherapiegroep werden de patiënten éénmalig met 12 Gray bestraald. Eindpunten van het onderzoek waren verbetering van de passageklachten, complicaties, kwaliteit van leven, het optreden van hernieuwde passageklachten en kosten. Patiënten werden geïncludeerd in 3 universitaire en 6 algemene ziekenhuizen in Nederland. De follow-up bestond uit huisbezoeken door een gespecialiseerde verpleegkundige op de tijdstippen 14 dagen, 1 maand en vervolgens maandelijks na de behandeling. In geval van complicaties of hernieuwde passageklachten werd de behandelend specialist geconsulteerd (**hoofdstuk 6**).

Hoewel er een snellere verbetering van passageklachten optrad na stentplaatsing, was de verbetering van passageklachten over de gehele periode beter na brachytherapie. Het totaal aantal complicaties was hoger in de stentgroep (33%) dan in de brachytherapiegroep (21%), voornamelijk door meer bloedingen in de stentgroep (13% vs. 5%). Het aantal behandelingen dat nodig was voor aanhoudende of hernieuwde passageklachten was gelijk in beide groepen (40% vs. 43%). Ook de mediane overleving was gelijk in beide groepen (**hoofdstuk 6A**).

Tijdens het onderzoek werden longitudinale data verkregen van zowel de generieke als ziekte-specifieke kwaliteit van leven. Ziekte-specifieke kwaliteit van leven werd bepaald aan de hand van de passageklachtenscore, de EORTC OES-23 wat een

vragenlijst is specifiek voor patiënten met slokdarmkanker, en een visueel analoge schaal waarop de mate van aanwezige pijnklachten kon worden aangegeven. Generieke kwaliteit van leven werd bepaald aan de hand van een vragenlijst specifiek voor kankerpatiënten, de EORTC QLQ-C30, en de EQ-5D die een index score geeft aan een bepaald gezondheidsprofiel en die een visueel analoge schaal bevat voor welbevinden. Kwaliteit van leven scores op de verschillende schalen waren beter na brachytherapy dan na stentplaatsing. Op de ziekte-specifieke EORTC OES-23 waren grote verbeteringen te zien op de 'passageklachten'- en de 'eten'-schaal na behandeling, maar de meeste kwaliteit van leven schalen verslechterden tijdens follow-up. De generieke kwaliteit van leven schalen gaven een betere weergave van het welbevinden en functioneren van de patiënt tijdens de follow-up dan de ziekte-specifieke kwaliteit van leven schalen (**hoofdstuk 6B**).

De initiële kosten voor brachytherapie waren lager dan voor stentplaatsing (brachytherapie: € 570 vs. stentplaatsing: € 1.500), echter de totale medische kosten waren gelijk voor beide behandelingen (brachytherpie: € 11.195 vs. stent: € 10.078). Het totaal aantal ligdagen in het ziekenhuis voor herbehandeling of ten gevolge van het ziekteproces tijdens follow-up was hoog in beide groepen: 12,4 dagen na brachytherapie en 11,5 dagen na stentplaatsing. Hierdoor waren de kosten voor intramurale zorg de grootste kostenpost (brachytherapy: € 7.982 vs. stent: € 6.512). Aangezien de totale kosten niet verschillend waren voor beide behandelingen, zullen de kosten niet een belangrijke rol spelen in de keuze voor de beste palliatieve behandelstrategie voor patiënten met slokdarmkanker (**hoofdstuk 6C**).

Zowel de voedselpassageklachten als kwaliteit van leven parameters waren meer beter na behandeling met brachytherapie dan na stentplaatsing voor de palliatieve behandeling van slokdarmkanker. Tevens traden er minder complicaties op na brachytherapie. Aangezien het aantal behandelingen in verband met aanhoudende en hernieuwde passageklachten en totale kosten niet verschilden tussen beide behandelingen zijn wij van mening dat deze groep patiënten bij voorkeur behandeld dient te worden met brachytherapie. Slechts als er sprake is van aanhoudende of hernieuwde passageklachten na brachytherapie als eerste behandeling is het plaatsen van een stent geïndiceerd. Stentplaatsing kan daarnaast overwogen worden als een snelle verbetering van passageklachten nodig is, zoals bij patiënten met ernstige ('totale') passageklachten of bij patiënten met een korte levensverwachting (**hoofdstuk 6**).

Om een inventarisatie te maken van het huidige beleid van diagnostiek en behandeling van slokdarmkanker, werd een enquête verricht onder alle specialisten met aandachtsgebied gastroenterologie (chirurgen, internisten en maag-darm-lever(MDL-) artsen) in Nederland. Bijna 90% van de specialisten gaf aan minder dan 20 patiënten per jaar te behandelen, meestal in het eigen ziekenhuis. CT was de meest gebruikte procedure voor nadere diagnostiek van slokdarmkanker, terwijl endoscopische ultrasonografie minder frequent werd gebruikt. Factoren die de keuze voor wel of geen operatie beïnvloedden, waren metastasen, lokale tumordoorgroei, slechte algemene conditie en een hoge leeftijd. Stentplaatsing was de meest gebruikte vorm van palliatie om passageklachten te verbeteren ten gevolge van slokdarmkanker. Deze enquête liet zien er een grote variatie is in de diagnostiek en behandeling van patiënten met slokdarmkanker. Er is behoefte aan een meer uniforme en 'evidence-based' aanpak voor de keuze van diagnostiek en behandeling van slokdarmkanker (**hoofdstuk 3**).

Voorafgaand aan het gerandomiseerde onderzoek tussen stentplaatsing en brachytherapie, werd een retrospectief onderzoek uitgevoerd naar de resultaten van 149 patiënten die behandeld werden met brachytherapie in de afgelopen 10 jaar in de Erasmus MC Rotterdam – Daniel den Hoed Kliniek. Brachytherapie werd toegediend als eenmalige (87%) dosis of in twee (13%) sessies, met een mediane toegediende stralingsdosis van 15 Gray. De passageklachtenscore verbeterde van een mediaan van 3 (vloeibaar) naar 2 (gemalen voeding), maar bij 51 (49%) patiënten trad geen verbetering op van de passageklachten. Procedure-gerelateerde complicaties traden op in 7 (5%) patiënten. Late complicaties, waaronder fistelvorming en bloedingen, ontstonden bij 11 (7%) patiënten. Twaalf (8%) patiënten hadden milde retrosternale pijn. De mediane overleving was 160 dagen. Tijdens follow-up ontwikkelden 55 (37%) patiënten hernieuwde passageklachten. Bij 34 (23%) patiënten werd een stent geplaatst ter verbetering van de (hernieuwde) passageklachten. Uit dit retrospectieve onderzoek werd geconcludeerd dat brachytherapie een veilige behandeling was aangezien er weinig complicaties optraden, maar de verbetering van passageklachten was matig effectief. Tevens hadden patiënten vaak aanhoudende of hernieuwde passageklachten waarvoor een aanvullende behandeling nodig was (**hoofdstuk 4A**).

Uit onze gerandomiseerde studie en de retrospectieve studie over brachytherapie bleek dat een nadeel van de brachytherapie was dat bijna de helft van de patiënten een aanvullende behandeling nodig had voor aanhoudende of hernieuwde

passageklachten. We onderzochten welke patiënten- en tumorkarakteristieken uit de studie invloed hadden op het optreden van aanhoudende of hernieuwde passageklachten na brachytherapie. Hieruit bleek dat dilatatie voorafgaand aan brachytherapie het risico op aanhoudende en hernieuwde passageklachten verhoogde. Tevens bestond er een trend voor een verhoogd risico op aanhoudende passageklachten bij patiënten die eerder een chemotherapeutische behandeling hadden ondergaan. Voor deze patiënten moeten alternatieve palliatieve behandelwijzen worden overwogen (**hoofdstuk 4B**).

Om de toepassing van stents voor de palliatie van het slokdarmcarcinoom te verbeteren, werden verschillende stent-gerelateerde problemen onderzocht. Een belangrijk discussiepunt bij de toepassing van stents was of een voorafgaande behandeling met radiotherapie en/of chemotherapie (RTCT) het risico op complicaties na stentplaatsing verhoogd. De invloed van voorafgaande RTCT op het resultaat van de stentplaatsing werd onderzocht in 200 prospectief vervolgde patiënten. Hiervan waren 49 patiënten behandeld met chemotherapie (n=35), radiotherapie (n=8) of beide (n=6). De incidentie van ernstige complicaties, hernieuwde passageklachten en de overleving was gelijk voor patiënten met of zonder voorafgaande RTCT. Retrosternale pijn kwam wel meer voor bij patiënten die een eerdere behandeling met RTCT hadden gehad voor de stentplaatsing (**hoofdstuk 5A**).

Ook na stentplaatsing is een veel voorkomend probleem het optreden van hernieuwde passageklachten. We onderzochten de oorzaken van stent-gerelateerde hernieuwde passageklachten, het moment van optreden na stentplaatsing, welke behandelingen werden toegepast en het succes van deze herbehandelingen. Bij 216 patiënten werd een stent geplaatst (Ultraflex: n=75, Flamingo Wallstent: n=71, Z-stent: n=70) voor de palliatie van passageklachten ten gevolge van slokdarmkanker. Bij éénderde van de patiënten traden hernieuwde passageklachten op, voornamelijk ten gevolge van tumorovergroei aan de boven- of onderrand van de stent, migratie van de stent, en een voedselbrok. Behandeling voor de stent-gerelateerde hernieuwde passageklachten was in het algemeen effectief en verbeterde de passageklachten. De meest effectieve behandeling voor tumorovergroei en stentmigratie was het plaatsen van een tweede stent. Bij stentmigratie kon de stent soms ook worden gerepositioneerd. Bij patiënten met hernieuwde passageklachten na stentplaatsing moet overwogen worden om deze te verwijzen voor een

endoscopie, aangezien het probleem bijna altijd effectief endoscopisch kan worden behandeld (**hoofdstuk 5B**).

Momenteel zijn er nieuwe typen stents ontwikkeld en nog in ontwikkeling die stent-gerelateerde problemen moeten voorkomen om zo de palliatie met stentplaatsing van slokdarmkanker te verbeteren. Stents die door de onderste slokdarmsfincter worden geplaatst, vergroten de kans op gastro-esophageale reflux. Onderzocht werd of de FerX-Ella stent met een anti-reflux mechanisme gastro-esophageale reflux kon voorkomen. Patiënten werden gerandomiseerd naar de FerX-Ella stent met anti-reflux klep (n=15) of de open FerX-Ella stent (n=15). Hieruit bleek dat de FerX-Ella stent wel een goede symptomatische verbetering van de passageklachten ten gevolge van slokdarmkanker gaf, maar dat het anti-reflux mechanisme de gastro-esophageale reflux niet kon voorkomen (**hoofdstuk 7**).

Toekomstige (gerandomiseerde) studies zullen moeten onderzoeken of de resultaten van de brachytherapie en stentplaatsing kunnen worden verbeterd met een hogere of gefractioneerde bestralingsdosis of met nieuwe typen stents zonder dat hiermee ook het aantal complicaties zal toenemen (**hoofdstuk 8**).

Dankwoord

Curriculum Vitae

Mijn grootste dank en vooral medeleven gaat uit naar de patiënten die hebben meegewerkt aan mijn onderzoek en hun familieleden. Slokdarmkanker is naar mijn mening één van de ergste ziekten die men kan krijgen. De diagnose wordt veelal te laat gesteld, waardoor enige hoop op genezing niet meer reëel is en de basisbehoefte van iedere mens, namelijk eten, wordt een voortdurende strijd. De verschillende wijzen waarop de patiënten met deze ziekte omgingen heeft mij gefascineerd. Ik heb geleerd dat alles relatief is in het leven en hoewel mensen het zich vaak niet meer realiseren, gezondheid blijft het grootste goed. Het heeft mij ook geleerd dat de medische begeleiding van deze mensen zeer belangrijk is, en ik zou hier graag in de toekomst mee door willen gaan.

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Curriculum Vitae

Marjolein Yvonne Véronique Homs werd geboren op 26 januari 1976 te Eindhoven en groeide op in Son en Breugel. Ze voltooide haar VWO aan het Bisschop Bekkerscollege te Eindhoven en ging in 1994 'Voeding en Gezondheid' studeren aan de Universiteit Wageningen. Tijdens haar studie voltooide ze een afstudeeronderzoek aan het Nederlands Kanker Instituut in het Antoni v Leeuwenhoekziekenhuis en ging een half jaar op stage naar de Nutrition Department van de Otago University in Dunedin, op het prachtige zuid-eiland van Nieuw Zeeland. Het laatste jaar van haar studie voltooide ze een onderzoek aan de Universiteit Wageningen en werkte daar als projectleider. Na haar afstuderen in 1999 als voedingskundige en epidemioloog reisde ze een half jaar door India en Nepal. Na deze avontuurlijke periode werkte ze korte tijd als junior onderzoeker bij de research afdeling van Unilever in Vlaardingen. In juli 2000 startte ze haar promotieonderzoek aan de afdeling Maag-, darm- en leverziekten van het Dijkzigt ziekenhuis, tegenwoordig Erasmus MC. Het onderzoek betrof de palliatieve behandeling van slokdarmkanker en vormde de basis voor dit proefschrift. Omdat ze echter in de toekomst klinisch onderzoek wil combineren met patiëntenzorg is ze in september 2003 gestart met de Master-opleiding Geneeskunde aan het Universitair Medisch Centrum Utrecht. Als eerste lichting van 16 studenten zullen ze binnen 4 jaar de opleiding geneeskunde gaan afronden inclusief co-schappen. Hierna wil ze zich verder specialiseren in de richting van de oncologie.