NURSE-LED FOLLOW-UP AND PALLIATIVE CARE OF ESOPHAGEAL CANCER PATIENTS

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If you can not be with the one you love,
love the one you are with

Stephen Stills

CONTENTS

1

General introduction and objectives

Approximately 400,000 patients are annually diagnosed world-wide with esophageal cancer, which makes this malignancy the eight most common cancer (1). The incidence of esophageal cancer has risen remarkably over the past two decades in the Western world, because of a marked increase in the incidence of adenocarcinoma (2, 3). 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% (4, 5). If a patient is able to undergo surgery and the tumor is considered resectable without evidence of distant metastases, a surgical resection is the primary treatment for esophageal cancer.

Despite recent advances in the curative treatment of esophageal cancer (6), more than 50% of patients with esophageal cancer have an inoperable disease at presentation. For these patients, only palliative treatment is possible. The goal of such treatment is to relief dysphagia, the case of much distress to these patients. Self-expanding metal stents are commonly used for the palliation of esophageal obstruction because of inoperable cancer. One of the drawbacks of the presently used stents is the high percentage of recurrent dysphagia due to stent migration and tissue in-/overgrowth. New stent designs have been developed that should overcome this unwanted sequel of stent placement. In addition, to overcome the problem of stent migration, large diameter stents have been introduced. The extra pressure on the esophageal wall exerted by large diameter stents, however, may cause more complications. Stents are effective for the palliation of esophageal cancer, particularly if the tumor is located in the mid or distal esophagus. Strictures of the proximal esophagus are more difficult to palliate. The use of stents in the proximal esophagus is, in particular, hampered by the risk of complications, the risk of compression on the trachea or patients intolerance.

Surgery for esophageal cancer is often accompanied by significant morbidity and affects patients quality of life (7-12). Follow-up after treatment of esophageal cancer mainly focuses on symptom control (13). It is well known that 30% of patients will develop recurrent cancer within the first year after an esophageal resection. For these patients, the prognosis is dismal and palliation of symptoms is usually the only treatment option. Common postoperative symptoms include dysphagia, weight loss, fatigue and a change in eating patterns. Particularly in the first year after an esophageal resection, physical limitations in normal daily life have been observed (8, 10). Treatment and counseling for these symptoms and problems are important issues during follow up after surgery for esophageal cancer. Over the last few years, the role of nurses in healthcare has been expanding (14). As previously, nurses are working to provide services which complement or extend those provided by physicians. Recently, however, some nurses are increasingly performing tasks and procedures performed by physicians (15-17). One of the items in which nurses are involved in advanced practice is in the development of nurse-led clinics in cancer care (18-21). Nurse-led follow-up may be an

alternative to regular control visits to the clinic for patients who have undergone treatment for esophageal cancer.

Objectives of this thesis:

Primary objective

- To compare follow-up of patients after esophageal cancer surgery by usual follow-up by surgeons in the outpatient clinic with regular home visits carried out by a specialist nurse with respect to health-related quality of life, patient satisfaction and costs.

Secondary objectives

- To survey the currently employed follow-up schedules after surgery for esophageal, gastric, pancreatic and colorectal cancer;
- To identify the role of nurses in endoscopy and gastroenterology;
- To identify and explore the experienced problems and expected care from professionals after esophageal resection;
- To compare the efficacy and safety of new stent designs with the most commonly used Ultraflex stent in patients with a malignant esophageal obstruction;
- To compared different types of small and large diameter stents for the risk of developing complications and recurrent dysphagia in patients with a malignant esophageal obstruction;
- To determine the efficacy and safety of stent placement in patients with a complicated malignant obstruction close to the upper esophageal sphincter.

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2

Follow-up after surgical treatment for cancer of the gastrointestinal tract

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ABSTRACT

Background: Presently, no evidence-based guidelines for the follow-up of patients after surgery for gastrointestinal cancer are available. As a consequence, follow-up strategies may differ between hospitals depending on preference of physicians. We investigated which follow-up procedures are currently employed after surgery for GI cancer in the Netherlands.

Method: A questionnaire was sent to all surgical departments in the Netherlands. The questionnaire focused on frequency of follow-up visits and diagnostic procedures after surgical treatment for oesophageal, gastric, pancreatic and colorectal cancer and psychosocial issues during follow-up.

Results: The response rate was 90% (83/92). In the majority of hospitals, surgeons treated patients with colorectal (100%) and gastric (96%) cancer in their own centre, whereas patients with pancreatic (64%) and oesophageal (61%) cancer were more often referred to a tertiary centre. For all patients treated for GI cancer, 3-4 follow-up visits were made in the first year, followed by at least 2 annual visits thereafter. After colorectal surgery, blood tests (78%), colonoscopy (75%) and abdominal ultrasound (57%) were frequently performed. In other GI malignancies, procedures were in most cases only performed if symptoms occurred. In almost three-quarter of patients, psychosocial problems were observed, which were dealt with by surgeons in two-thirds of patients. The majority of patients treated for GI cancer were pre- and postoperatively discussed in a multidisciplinary setting. Oncologists, gastroenterologists and dieticians were the most frequently consulted specialists after surgery for GI cancer.

Conclusion: Patients frequently visit the outpatient clinic after surgery for GI cancer in the Netherlands. Whereas follow-up after colorectal cancer surgery focuses on finding recurrent disease and metachronous lesions in the colorectum, this is less clear after oesophageal, gastric and pancreatic cancer surgery. Further studies are needed to establish what the most effective follow-up protocol after different types of GI cancer surgery.

INTRODUCTION

Of all cancers in the gastrointestinal (GI) tract seen in the European Union, colorectal cancer most frequently occurs with an incidence of 280,000 cases per year. The incidence rates of gastric, pancreatic and oesophageal cancer are respectively 89.000, 55.000 and 31.000 per year (1).

The optimal follow-up strategy for patients after surgery of cancer in the GI tract has not been defined (2-4). During follow-up visits, attention mainly focuses on the detection of symptoms from the previous treatment, and on the detection of recurrent or metachronous cancer. Several studies have reported that screening programs after GI cancer surgery may contribute to early detection of second primaries. Particularly, it has been suggested that early detection of malignant lesions in the otolaryngeal area after oesophageal cancer surgery (5), cancer in the gastric remnant after gastric cancer surgery (6, 7), and metachronous lesions in the colon after colorectal cancer surgery (8, 9) may have a positive impact on survival. Other studies have suggested that the benefit of scheduled routine follow-up after treatment of gastric and colorectal cancer surgery is however not evidence-based (10, 11). Moreover, it has been reported that recurrent malignant disease may occur between scheduled follow-up visits (12, 13).

With regard to follow-up after surgical treatment of GI cancer, presently available guidelines (2, 4, 13-21) give no clear recommendations when, how and in which frequency follow-up should be performed. To survey the currently employed follow-up schedules after surgery for oesophageal, gastric, pancreatic and colorectal cancer in the Netherlands, a questionnaire was sent to all surgical departments.

MATERIALS AND METHODS

In July 2004, a questionnaire was sent to all surgical departments in the Netherlands (n=92). After 4 weeks, a reminder was sent. A total of 83 (90%) questionnaires were returned.

Methods

The questionnaire (see Appendix) contained 10 items, all multiple choices. The first three questions involved general characteristics of the participating surgeons, including their period of registration as medical specialist, type of hospital (university or general hospital), and the number of patients with oesophageal, gastric, pancreatic, and colorectal cancer that were diagnosed and treated annually in their department. Questions 4-10 were selective questions on oesophageal, gastric, pancreatic, and colorectal cancer and investigated a) proportion of GI cancer patients discussed in a multidisciplinary setting; b) the frequency of follow-up visits in the first year after surgery; c) the type of medical tests and/or procedures

performed during or as a result of the follow-up visits; d) the percentage of patients with encountered psychosocial problems, and the percentage of time spent on support and advice for this; and e) whether and to what extent other disciplines or specialists were involved during follow-up.

Statistical analysis

We used descriptive statistics to analyse the frequencies. The answers 'if indicated' and 'do not know' were categorised together. The chi-square test was used for analysing the relationship between type of hospital on the one hand, and the number of treated patients for a particular GI cancer, the frequency of follow-up visits, procedures performed during follow-up visits, and involvement of other disciplines/specialists on the other hand. A p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 11.1 (SPSS Inc., Chicago, IL, USA).

RESULTS

Surgical departments of 75 general hospitals and 8 university hospitals returned the questionnaire.

In 65% (54/83) of hospitals, surgeons diagnosed annually one or more new patients with oesophageal cancer. With regard to gastric, pancreatic and colorectal cancer, these percentages were 86% (71/83), 74% (61/83) and 96% (80/83), respectively. The majority of surgeons treated patients with colorectal (83/83; 100%) and gastric cancer (79/83; 95%) in their own hospital, whereas patients with pancreatic (30/83; 36%) or oesophageal cancer (32/83; 39%) were less frequently treated in their own hospital and more often referred to specialised centres ($p=0.007$ and $p=0.013$, respectively).

For all GI cancers, the frequency of follow-up visits was at least 3-4 visits in the first year (60-84%). In the second and following years, follow-up visits were less frequently performed, however, in the majority of patients (65-77%) this was still at least two visits per year (Table 1).

During follow-up, physical examination was frequently performed after resection of oesophageal (77%), gastric (87%), pancreatic (74%) and colorectal cancer (98%) (Figure 1a). After surgery for gastric cancer, a full blood count and an upper GI endoscopy was performed in 25% of hospitals (Figure 1b). After resection of pancreatic cancer, a full blood count was only performed in 17% of hospitals (Figure 1b). Frequently used procedures after colorectal cancer surgery were a full blood count (78%) (Figure 1b), and colonoscopy (75%). In addition, abdominal ultrasound was regularly applied in 57% of hospitals, whereas a CT scan was only used in 8% of hospitals during follow-up (Figure 1c-1d). With regard to procedures performed during follow-up visits, there were no differences between surgical departments in general or university hospitals.

Table 1. Frequency of follow-up visits in the first year after treatment and from one year after surgery for GI cancer, in 83 hospitals in the Netherlands

	Oesophageal cancer n=51		Gastric cancer n=79		Pancreatic cancer n=53		Colorectal cancer n=83	
Follow-up visits in the first year; no. of hospitals (%)								
0-2	7	(14)	6	(7)	10	(19)	2	(3)
3-4	31	(61)	63	(80)	32	(60)	70	(84)
> 4	13	(25)	10	(13)	11	(21)	11	(13)
Follow-up visits from one year; no. of hospitals (%)								
0-2	33	(65)	61	(77)	38	(72)	63	(76)
3-4	15	(29)	14	(18)	12	(22)	14	(17)
> 4	3	(6)	4	(5)	3	(6)	6	(7)

Psychosocial problems were encountered in three-quarter of hospitals after surgery for oesophageal cancer (75%), gastric cancer (65%), pancreatic cancer (72%), and colorectal cancer (72%). In half of the hospitals (47-55%), surgeons spent more than 50% of time on advice for these problems to patients after GI cancer surgery.

The majority of patients surgically treated for cancer of the oesophagus (96%), stomach (91%), pancreas (94%) and colon (90%) had been discussed in a multidisciplinary setting. This

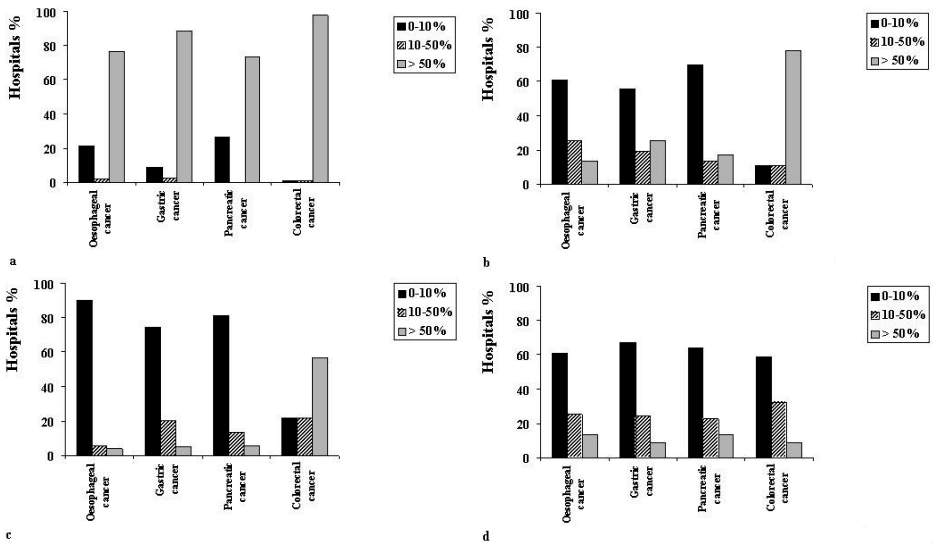

Figure 1: Investigations (a. physical examination; b. blood count; c. abdominal ultrasound; d. ct-scan) performed during follow-up visits after treatment for oesophageal cancer (n=51); gastric cancer (n=79); pancreatic cancer (n=53); and colorectal cancer (n=83) in 83 hospitals

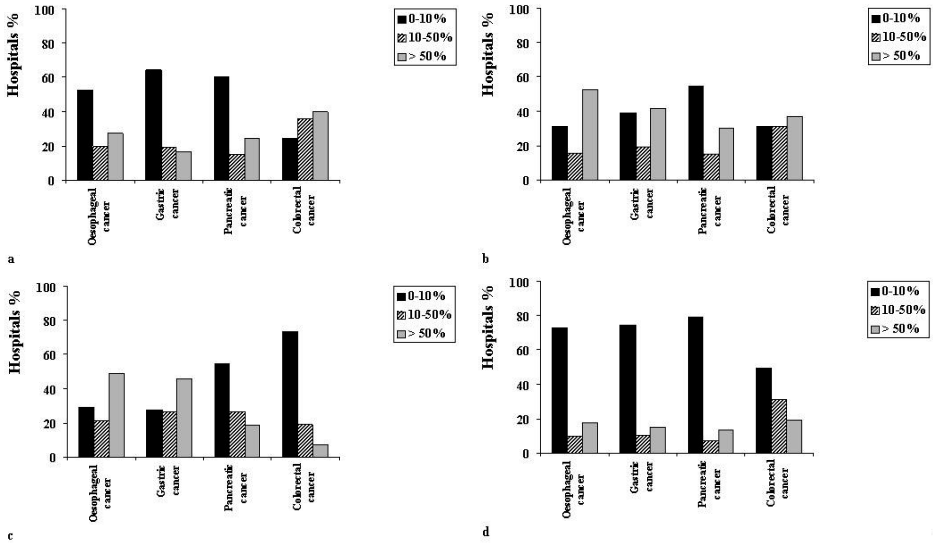

Figure 2: Disciplines (a. oncologist; b. gastroenterologist; c. dietician; d. nurse specialist) involved during follow-up of patients after treatment for oesophageal cancer (n=51); gastric cancer (n=79); pancreatic cancer (n=53); and colorectal cancer (n=83) in 83 hospitals

was not different between general and university hospitals. Oncologists, gastroenterologists and dieticians were the most frequently consulted medical or non-medical specialists during follow-up of patients after surgery for GI cancer (Figures 2a-c). Following surgery for colorectal cancer, nurse specialists were often involved, in most cases this was a stoma therapist nurse (Figure 2d).

DISCUSSION

This survey, with a response rate of 90% of surgical departments in the Netherlands, showed that GI cancer surgery is performed in university as well as in general hospitals, however, patients with oesophageal cancer and pancreatic cancer are more commonly referred to specialised centres. This suggests that in the Netherlands many surgeons comply with recently presented evidence that pancreatic and oesophageal cancer surgery should be concentrated in high-volume centres with ample experience in the procedures and optimal pre- and postoperative care for these patients (22). However, the findings of this questionnaire also suggest that almost 40% of hospitals consider their expertise to be optimal enough to treat these patients in their own centre.

In the literature, follow-up frequencies, varying between 3 and 11 visits per year, have been reported during a follow-up period of 5 years or more after surgery for GI malignancies (5, 8-12, 23-25). The optimal time interval of follow-up after GI cancer surgery is, however, unknown, and largely depends on the nature and severity of symptoms and complications after surgery, and also on the possibility that early detection of metastases will result in a treatment with curative intent (2, 13). However, in many cases, the finding of recurrent cancer indicates that palliation of symptoms is the only treatment option, especially following oesophageal, gastric and pancreatic cancer surgery (2, 19). Early detection of small and therefore resectable liver metastases after treatment for colorectal cancer may be an exception and has been demonstrated to offer a chance for cure to these patients (13).

In the present study, in the majority of hospitals, physical examination was performed during follow-up after surgery for oesophageal cancer, gastric cancer and pancreatic cancer, and further diagnostic procedures were only performed if patients developed symptoms indicating the possibility of recurrent cancer (Figures 1a-d). The frequent use of physical examination is not surprising, as the results of this, along with a patients' history, may be the reason to perform additional diagnostic procedures. According to the literature, if indeed follow-up procedures are being performed after surgery for oesophageal, gastric and pancreatic cancer, it is recommended to perform a full blood count (20) and/or a chest X-ray at 4-month intervals (14-16). In order to detect a second primary malignancy after treatment for oesophageal squamous cell carcinoma, some recommend an intensive follow-up schedule including CT-scan of the chest, upper GI endoscopy and otolaryngeal examination (5). A periodical surveillance endoscopy and biopsy is recommended to detect early cancer in the gastric remnant (6, 7). It has so far not been demonstrated that all these types of procedures are cost-effective in patients after oesophageal, gastric and pancreatic cancer surgery, if indeed performed on a routinely basis (10).

Following treatment of colorectal cancer, there is no agreement whether, and if so, which tests should be performed (4). In the present survey, in the majority of hospitals, physical examination (98%), full blood count (78%), colonoscopy (75%), and abdominal ultrasound (57%) were performed (Figure 1a-c). It is not clear why CT-scanning was only performed in 8% of hospitals. However, it could suggest that abdominal ultrasound is considered to be sensitive enough to detect liver metastases. According to the literature, it has been proposed to perform follow-up in patients after colorectal cancer, including additional investigations, according to a systematic follow-up schedule (8, 26, 27), to identify metachronous lesions and to detect resectable liver metastases. Others have recommended follow-up only in case of signs and symptoms of recurrent cancer (17, 24, 25), or in patients considered at high risk of recurrence, such as the presence of an adenocarcinoma located in the proximal colon or if the pre-operative carcinaembryonic antigen (CEA) level is elevated (23, 25). If indeed follow-up examinations are being performed after colorectal cancer surgery, several guidelines can be followed; these vary between colonoscopy at yearly intervals to every 3-5 years (13, 21,

28) and CEA blood tests every 3-6 months to annually (21) or to only once every 5 years (28). In order to detect resectable liver metastases, liver imaging by ultrasound or CT-scanning should be performed at least once during the first 2 years after colonic resection (13).

Complications and symptoms after GI cancer surgery very likely influence patients' psychosocial functioning. Recently, psychosocial problems have been acknowledged to be an important surgical outcome measure (29). It was demonstrated in this survey that almost three-quarter of patients after GI cancer surgery have psychosocial problems. As a consequence of this, in half of the Dutch hospitals, surgeons spent a considerable amount of time in dealing with these problems. Over the last few years, nurse practitioners (NP) have been increasingly involved in the care of patients with malignancies (30). It seems therefore logical to investigate in future studies whether nurses could play a role in the follow-up of patients with GI cancer, not only for psychosocial support and advice, but also in the management of patients in whom the detection of metastases means that only a palliative therapy is possible.

Although most GI cancer patients in The Netherlands are being discussed in a multidisciplinary setting, both pre- and postoperatively, other specialists or disciplines are often not involved in the care of these patients during follow-up (Figures 2a-d). The only exceptions are colorectal cancer patients, who are regularly seen by oncologists (Figure 2a). This is in line with the increased use of chemo radiotherapy in this malignancy (31). A multidisciplinary postoperative approach in the treatment of GI cancer is, however, recommended to avoid the duplication of follow-up visits, examinations and diagnostic procedures with incumbent inconvenience to patients (2).

In conclusion, patients frequently have scheduled visits to the outpatient clinic after surgical treatment for oesophageal, gastric, pancreatic and colorectal cancer in the Netherlands. Except for colorectal cancer, follow-up after treatment of GI cancer mainly focuses on symptom control. Presently, it is still unclear whether, and if so, which tests and/or procedures should be performed for the detection of early recurrences. Randomised trials are needed to demonstrate the diagnostic and cost efficacy of follow-up procedures. In addition, further studies are therefore needed to investigate what type of follow-up and by which medical discipline (physicians or nurses) will improve quality of life and possibly even survival in patients after a resection of GI cancer.

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APPENDIX

Questionnaire

1. Are you working in an university hospital or general hospital?
   - ○ University hospital
   - ○ General hospital

2. How long have you been registered as a medical specialist?
   - ○ 0-5 year
   - ○ 5-10 year
   - ○ 10-20 year
   - ○ > 20 year

3. a) How many patients with gastrointestinal (GI) cancer do you diagnose annually?
      1) Oesophageal cancer 0 / <5 / 5-20 / 20-50 / >50
      2) Gastric cancer 0 / <5 / 5-20 / 20-50 / >50
      3) Pancreatic cancer 0 / <5 / 5-20 / 20-50 / >50
      4) Colorectal cancer 0 / <5 / 5-20 / 20-50 / >50

   b) How many patients do you treat annually?

   See answer categories in question 3a

4. How many patients (%) diagnosed and treated for GI cancer are discussed in a multidisciplinary setting?
   1) Oesophageal cancer 0-10% / 10-50% / 50-90% / >90%
   2) Gastric cancer 0-10% / 10-50% / 50-90% / >90%
   3) Pancreatic cancer 0-10% / 10-50% / 50-90% / >90%
   4) Colorectal cancer 0-10% / 10-50% / 50-90% / >90%

5. How often do patients visit the outpatient clinic in the first year after surgery?
   1) Oesophageal cancer 0 / 1 / 2 / 3-4 / 5-6 / >6
   2) Gastric cancer 0 / 1 / 2 / 3-4 / 5-6 / >6
   3) Pancreatic cancer 0 / 1 / 2 / 3-4 / 5-6 / >6
   4) Colorectal cancer 0 / 1 / 2 / 3-4 / 5-6 / >6

6. How often do patients visit the outpatient clinic from one year after surgery?

   See answer categories in question 5

7. What type of procedures do you employ during or in response to the follow-up visits?

   A = 0-10% C = 50-90%

   B = 10-50% D = > 90%

	Oesophageal cancer	Gastric cancer	Pancreatic cancer	Colorectal cancer
Physical examination				
Blood tests				
Chest x-ray				
Abdominal x-ray				
Abdominal ultrasound				
CT-scan				
Gastroscopy				
Colonoscopy				
Swallow x-ray				
Other, …….				

8. In how many patients (%) do you identify psychosocial problems?

   See answer categories in question 4

9. How much of your time (%) do you spend on psychosocial support during follow-up visits?

   See answer categories in question 4

10. Which other specialists or disciplines do you consult during follow-up?

    A = 0-10% C = 50-90%

    B = 10-50% D = > 90%

	Oesophageal cancer	Gastric cancer	Pancreatic cancer	Colorectal cancer
Oncologist				
Gastroenterologist				
Nurse specialist				
Dietician				
Social worker				
Psychologist				
Other, …….				

3

Nurses working in gastrointestinal endoscopic practice: a review

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ABSTRACT

Background: Over the last 10 years, nurses increasingly perform tasks and procedures which were previously performed by physicians. In this review, we investigated what types of gastrointestinal care and endoscopic procedures nurses presently perform and reviewed the available evidence regarding the benefits of these activities.

Methods: Review of published articles on nurses' involvement in gastrointestinal and endoscopic practice.

Results: In total, 19 studies were identified that evaluated performance and participation of nurses in gastrointestinal and endoscopic practice. Of these, three were randomized trials on the performance of nurses in flexible sigmoidoscopy (n=2) and upper endoscopy (n=1). Fourteen non-randomized studies evaluated performance in upper endoscopy (n= 2), endoscopic ultrasound (n=1), flexible sigmoidoscopy (n=7), capsule endoscopy (n=2) and percutaneous endoscopic gastrostomy placement (n=2). In all studies, it was found that nurses accurately and safely performed these procedures. Two further studies demonstrated that nurses adequately managed follow-up of patients with Barrett's esophagus and inflammatory bowel disease. Four of the 19 studies showed that patients were satisfied with the type of care nurses provided. Finally, it was suggested that costs were reduced if nurses performed a sigmoidoscopy and evaluated capsule endoscopy examinations compared to physicians performing these activities.

Conclusion: The findings of this review support the involvement of nurses in diagnostic endoscopy and follow-up of patients with chronic gastrointestinal disorders. Further randomized trials are, however, needed to demonstrate whether this involvement compares at least as favorably with gastroenterologists in terms of medical outcomes, patient satisfaction, and costs.

INTRODUCTION

Changes in health care have been challenging for professionals and patients, and increasing demands in care are providing the impetus for the expanding scope of nursing practice. Over the last few years, the role of nurses in healthcare has been expanding (1). As before, nurses are working to provide services that complement or extend those provided by physicians. Recently, however, some nurses increasingly work as physician substitutes, performing tasks and procedures previously performed by physicians (2). These nurses practice in a variety of settings with specialized expertise, e.g., oncology (3), geriatrics (4), primary care (5), obstetrics (6), neonatology (7), emergency care (8, 9), and surgery (10). In the field of gastroenterology, clinical nurse specialists and nurse practitioners are similar terms for registered nurses who have completed an advanced degree in nursing and are qualified in gastroenterology nursing. A few reports discuss the role of these nurses in gastroenterology and endoscopy (11, 12). Particularly with regard to screening for colorectal cancer, it was concluded that nurses may contribute to the prevention and early detection of this malignancy (13-15). Nevertheless, the number of studies that clearly and objectively identified the potential benefits of nurses as care providers in a gastroenterology setting is limited.

The aim of this review was to identify the types of gastrointestinal tasks and endoscopic procedures provided by nurses complementary to or substituting physician activities, and to review the available evidence regarding the benefits of this role in the gastrointestinal setting.

METHODS

We reviewed the literature from the databases PubMed and ISI Web of Science. Because the role of nurses in gastroenterology and endoscopy has been more specifically developed since the late 1990s, we only considered the time period January 1990 to June 2006 for this review. Four study types were eligible for inclusion:

- Randomized controlled trials (RCT): random allocation of patients to an intervention or control group;
- Controlled trials (CT): the intervention group is compared with a control group selected by a non-random process, or the intervention is followed and/or controlled through a second procedure by a gastroenterologist;
- Prospective studies (PS): prospective evaluation of the intervention; no control group;
- Retrospective studies (RS): retrospective evaluation of the intervention.

Two authors (EMLV/PDS) extracted the data and assessed the study quality according to the schedule in Table 1. Participants in different studies were gastroenterologists, residents, and qualified nurses working as a substitute to a gastroenterologist or as gastroenterologist

Table 1. Classification of methodological quality of studies

A1	Systematic review, which includes at least two independently performed studies on A2 level.
A2	High-quality randomized double blind controlled trial.
B	Comparative study, fulfilling not all characteristics of A2
C	Noncomparative study
D	Opinion of experts

supplements. This last group included, for example, nurse practitioners, clinical nurse specialists, advanced practice nurses, and registered nurses. Because the job title, education and experience of nurses vary among and within countries, we did not select nurses by job title.

The following keywords were used: advanced practice nurse, nurse practitioner, variations on the word "nurse", Barrett's esophagus, esophageal cancer, esophagus, cancer screening, gastric cancer, stomach, inflammatory bowel disease, IBD, Crohn's disease, ulcerative colitis, colon, colorectal carcinoma, pancreas, pancreatic carcinoma, liver, hepatocellular carcinoma, liver transplantation, hepatitis, endoscopy, sigmoidoscopy, gastroscopy, colonoscopy, gastroenterology, dyspepsia, reflux, irritable bowel syndrome and IBS. Also, reference lists of published articles were investigated. Systematic reviews, non-English language articles, and studies only published in abstract form were excluded.

RESULTS

Description of studies

Nineteen studies were identified that evaluated the performance and participation of nurses in gastroenterology and endoscopy (Table 2) (16-34). Of these, three were RCT (16-18), eight were CT (19-26), six were PS (27-32) and two were RS (33, 34). Assessment of the methodological quality of the studies is shown in Table 2. In 13 studies, nurses performed an endoscopic procedure, i.e., esophagoscopy (19), upper endoscopy (16, 20), endoscopic ultrasonography (EUS) (27) and flexible sigmoidoscopy (FS) (17, 18, 21-23, 28-31). In two studies, nurses interpreted video capsule endoscopy (VCE) (26, 32). In two other studies, nurses assisted in the placement of a percutaneous endoscopic gastrostomy (PEG) catheters (24, 25). Finally, in two studies, nurses were responsible for managing patients with gastrointestinal disorders, i.e., inflammatory bowel disease (IBD) (33) and Barrett's esophagus (BE) (34).

Upper gastrointestinal endoscopy

One randomized study compared the adequacy and accuracy of diagnostic upper gastrointestinal endoscopy performed by five medical and two nurse endoscopists (16). The videotaped procedures were assessed by a gastroenterologist blinded to the identity of the endoscopist. An adequate view was obtained in 53% of doctors endoscopies and 92% of

Table 2. Nurses in gastroenterology and endoscopy: interventions and outcomes

Upper gastrointestinal endoscopie						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Meaden et al. (2006)	RCT	A2	367 patients 2 nurses 4 GI physicians 1 physician	Upper GI endoscopy	Adequate view doctors v.s nurses: 53% vs.92% (95% CL 31, 47%); Agreement expert doctors v.s nurses: 81% vs. 78% (95% CL -1%, 6%); No differences in rate of biopsy performance; No differences in missed lesions (mostly gastritis);	Registered nurse
Smale et al. (2003)	CT	B	480 patients 2 nurses 7 GI physicians	Upper GI endoscopy	Nurses vs. physicians: no differences pre-procedure anxiety (p=0.61),discomfort during intubation (p=0.97), discomfort during examination (p=0.90), post-procedure examination rating (p=0.79);	Registered nurse
Wildi et al. (2003)	CT	B	40 patients 1 nurse 1 GI physician	Esophagoscopy	Small-caliber endoscopy by nurse vs. video-endoscopy by physician: sensitivity 75% vs. 95 % (CI: 67%-82%), specificity 98% vs. 95% (CI: 96%-99%); Nurse: missed all 4 of esophageal rings;	Nurse practitioner
Endoscopic Ultrasonography (EUS)						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Meenan et al. (2003)	PS	C	300 patients 1 nurse 4 GI physicians	Training program EUS	Nurse showed a comparable degree of competence in mediastinal scanning (12.5/18 points vs. 18/18, 16.6/18, 15.7/18 and 11.8/18 points, resp.);	Registered nurse
Flexible sigmoidoscopy (FS)						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Basnyat et al. (2002)	PS	C	706 patients 1 nurse	FS, nurse-led service	Cause for bleeding identified in 642/706 (91%) patients; Satisfaction with service: 246/249 (99%) patients; Cost reduction: $ 80;	Registered nurse
DiSario & Sanowski (1993)	RCT	B	212 patients 5 nurses 5 residents	Training program FS	Nurses vs. residents: no differences in missing lesions (total miss rate 4/250 lesions, 1.6%), mean insertion depth (46 cm vs. 44cm), and mean procedure time (16 min. vs. 16 min.); 1/5 nurses achieved no proficiency;	Registered nurse Practice nurse
Goodfellow et al. (2003)	PS	C	282 patients 1 nurse	FS, nurse-led service	Abnormalities identified in 217/282 (77%) patients; 1/161 (1%) lesions missed compared with back-to-back double-contrast barium enema;	Nurse practitioner

Maule (1994)	CT	B	2611 patients 4 nurses 2 GI physicians	FS	Nurses missed 1/269 (0.3%) lesions; Mean insertion depth: nurse 39 cm, physician 45 cm (p=0.001); Patients' discomfort: physicians more cramping (p=0.001); No correlation between cramping and insertion depth;	Registered nurse Practice nurse
Schoenfeld et al. (1999)	RCT	A2	313 patients 3 nurses 4 GI physicians	FS	Miss rate adenomatous polyps: nurse 3/14 (21%), physician 6/30 (20%) (p=0.91); Miss rate all polyps: nurse 22/128 (17%), physician 41/139 (29%) (p=0.02); Mean insertion depth: nurse 55 cm, physician 61 cm (p<0.00001);	Registered nurse
Schoenfeld et al. (1999)	CT	B	383 patients 1 nurse 3 surgeons 3 GI physicians	FS	Detection rate adenomas: nurses 8/114 (7%), surgeons 11/139 (8%), physicians 12/130 (9%) (p=0.81); Mean insertion depth: nurses 53 cm, surgeons 50 cm, physicians 54 cm (p=0.01); Mean procedure time: nurses 8.3 min., surgeons 7.6 min., physicians 6.8 min. (p=0.0001); Satisfaction: overall no differences (p=0.60);	Registered nurse
Schroy et al. (1988)	PS	C	100 patients 1 nurse 1 GI physician	FS	Endoscopy by nurse vs. physician's review: sensitivity 75%, specificity 94%; 8/36 (22%) lesions identified only by physician, 4/36 (11%) lesions identified only by nurse;	Nurse practitioner
Shapero et al. (2001)	PS	C	488 patients 2 nurses 1 GI physician	FS	Nurses identified 75/488 (15%) lesions;	Registered nurse
Wallace et al. (1999)	CT	B	3701 patients 1 nurse 2 physician assistants 15 GI physicians	FS	Mean insertion depth: non-physicians (incl. 1 nurse) 52 cm, physicians 55 cm (p<0.001); Detection rate polyps: non-physicians 619/2323 (27%), physicians 321/1378 (23%) (p=0.34); Detection rate neoplastic polyps: non-physicians 180/2323 (8%), physicians 80/1378 (6%) (p=0.35); Cost reduction: $97	Nurse practitioner
Video capsule endoscopy (VCE)						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Levinthal et al. (2003)	CT	B	20 patients 1 nurse 1 GI physician	VCE	Miss rate lesions: nurse 2/27 lesions (sensitivity 93%, CI 74-99%), physician 3/27 lesions; Nurse: emptying time and time of passage ileocecal valve within 1 min. from time physician in 18/20 patients (agreement 90%, CI 67-98%);	Registered nurse

Niv & Niv 2005	PS	C	50 patients 1 nurse 1 GI physician	VCE	Complete agreement in 12 cases interpreted as normal; Thumbnail selection: nurse 130 vs. physician 99, agreement in 93/96 (97%) cases; Miss rate: nurse 3 in 3 patients, physician 4 in 3 patients; Mean computed transit time gastric and small bowel: nurse 26 and 304 min., resp., physician 26 and 318 min., resp.; Mean reading time: nurse 100 min. vs. physician 59 min.; Mean reading time after thumbnail selection: 10 min.; Cost reduction: $ 324	Nurse practitioner
Percutanous endoscopic gastrostomy (PEG)						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Patrick et al. (1996)	CT	B	35 patients 1 nurse 3 GI physicians	PEG, nurse-assisted	Complications: nurse 0/20 (0%), physicians 0/15 (0%);	Registered nurse
Sturgess et al. (1996)	CT	B	100 patients 1 nurse 3 GI physicians	PEG, nurse-assisted	Complications: nurse 2/50 (4%), physician 2/50 (4%); 30-day mortality: nurse 4/50 (8%), physician 6/50 (12%);	Nurse practitioner
Management of gastrointestinal disorders						
References	**Design**	**Classification of study**	**Participants**	**Intervention**	**Results**	**Nurse title**
Nightingale et al. (2000)	RS	C	344 patients 1 nurse	IBD nursing service	38% reduction of hospital visits; 19% reduction of in-hospital stay; Patients in remission increased from 63% to 69%; Satisfaction: improvement on information giving ($p<0.001$), and advice on maintaining health ($p<0.001$);	Nurse specialist
Schoenfeld et al. (1998)	RS	C	123 patients 1 nurse	Treatment of BE, nurse-directed	Variation from guidelines: interval between surveillance endoscopy 5/269 (1.9%) events, treatment of reflux 7/358 (1.3%) events; Satisfaction: overall care 90/102 (88%) patients, questions answered 90/102 (88%) patients, patient education 87/102 (76%) patients;	Registered nurse

RCT=randomized controlled trial; CT=controlled trial; PS=prospective study; RS=retrospective study; IBD=inflammatory bowel disease; BE=Barrett's esophagus; GI=gastrointestinal

nurses (difference 38%; 95% CL 31%, 47%). In adequately viewed areas, the mean agreement between doctor and expert and nurse and expert was 81% and 78%, respectively (difference 8%; 95% CL -1%, 6%). The types of lesions missed, most commonly gastritis, were similar for doctors and nurses. There was no difference between doctors and nurses in the rate of biopsy performance (90% vs. 91%; p=0.86).

Wildi et al. (19) investigated nurse-led screening for esophageal disorders. In this study, a nurse performed esophagoscopy in 40 patients with a small-caliber endoscope, followed by a standard endoscopy performed by a supervising gastroenterologist. Both the nurse practitioner and the gastroenterologist were blinded to each other's findings. Sensitivities of small-caliber esophagoscopy by the nurse and standard endoscopy by the gastroenterologist for detecting abnormalities were 75% and 95% (95% CI: 67%-82%), respectively, whereas specificities were 98% and 95% (95% CI: 96%-99%), respectively. Particularly, nurses underestimated the presence of esophageal rings. Because two different types of endoscopes were used, it became unclear whether the lower sensitivity was explained by the use of the small-caliber endoscope or by the performance of the nurse.

Smale et al. (20) studied 480 patients who underwent upper gastrointestinal endoscopy performed by two nurses and seven physicians, and assessed sedation requirements and patients' anxiety, discomfort, satisfaction and attitude towards future sedation. No differences were found in preprocedural anxiety, discomfort during introduction of the endoscope and during the further procedure, or postprocedural examination rating between nurses and physicians.

EUS

Meenan et al. (27) investigated a training program for EUS. Apart from four senior fellows in gastroenterology, one nurse was also trained. Examinations performed by the nurse were limited to views of the esophagus and proximal stomach, whereas the physicians also examined the duodenum. Assessment of the ability to perform EUS was judged by an experienced endosonographer using a point-score system. A total of 18 points were awarded for the ability to produce 'best views with certainty'. After 25 examinations, the nurse showed a comparable degree of competence (mean score of 12.5/18 points) in evaluating the mediastinum to that of the other trainees (18/18; 16.6/18; 15.7/18 and 11.8/18, respectively).

Flexible sigmoidoscopy

Nine studies investigated FS performance by nurses in terms of accuracy, efficacy and safety (17, 18, 21-23, 28-31). The miss rate of lesions was reported in two randomized studies (17, 18). This was determined by the supervision of all FS procedures by a qualified endoscopist in one study (17), and by back-to-back endoscopy by a senior gastroenterologist in another study (18). The nonrandomized studies reported detection rate of lesions (21-23, 28-31) (Table 2).

In one of the two randomized studies, 260 patients were randomized to undergo FS performed by a nurse (n=5) or by a resident (n=5) (17). Early in the training, three small polyps and one diverticulum were missed (1.6% of 250 lesions) by 3 nurses and 1 resident each. Mean insertion depth of FS performed by trainees was 44 cm compared with 46 cm in nurses. One nurse did not achieve proficiency after 35 procedures. No differences were observed in procedure tolerance among patients examined by nurses and residents. In the second randomized study, 328 patients were randomized to undergo screening FS performed by a nurse or a gastroenterologist (18). Within 5 minutes of completion of the first FS, a second FS was performed. The gastroenterologist who performed the second endoscopy was blinded to the type of endoscopist. Gastroenterologists inserted the sigmoidoscope further than nurses (61 vs. 55 cm, respectively; $p<0.00001$). Although gastroenterologists missed more polyps (29% vs. 17%; $p=0.02$), gastroenterologists and nurses had a similar frequency in missing adenomatous lesions (20% vs. 21%; $p=0.91$).

Maule (21) compared 1881 FS procedures performed by four nurses with 730 procedures performed by two physicians. No differences were found in the detection rate of adenomas and colorectal cancers between nurses and physicians. In this study, discomfort and perception of patients undergoing FS procedures was also measured. Of the measured variables, only cramps were more frequently experienced by patients if performed by physicians compared with nurses ($p=0.001$). Although physicians had a greater mean depth of insertion (39 cm vs. 45 cm; $p=0.001$), there was no correlation between cramps and insertion depth.

In two prospective studies, consecutive patients were assigned to have FS performed by the first available endoscopist, i.e., a nurse, a physician assistant, a surgeon or a GI physician (22, 23). No differences were observed in the detection of adenomas (Table 2). In one study, the mean insertion depth was less for surgeons compared with the nurse and gastroenterology fellows (50 vs. 53 vs. 54 cm, respectively; $p=0.01$) (22). In the second study, the mean depth of FS performed by nonphysicians (nurse or physician assistant) was 52 cm compared with 55 cm in physicians ($p<0.001$) (23). Patient satisfaction was measured in one of these studies by a questionnaire (22). Although the nurse received better scores on some of these scales than the physicians, no differences were detected for overall satisfaction, communication, and technical and interpersonal skills between both types of endoscopists.

In four studies, FS procedures performed by five nurses were recorded on a videotape and reviewed by three physicians to validate the results (28-31). It was reported that FS performed by nurses was effective and safe (Table 2).

Basnyat et al. (30) evaluated a nurse-led open-access FS service for patients with rectal bleeding. A cause of bleeding was identified in 642/706 (91%) patients. Underlying pathologies that accounted for rectal bleeding were found in 171 (24%) patients and these included polyps, IBD, solitary rectal ulcer syndrome, and colorectal cancer. Ninety-nine percent of the first 249 patients were satisfied with the performance of nurses and indicated that they received adequate information before to undergoing the procedure. In another study, the

investigators reported that 99% of the nurse-led procedures were classified as being successful, whereas, in 77% of patients abnormalities were identified (31). Only 9/249 (4%) patients had moderate discomfort, whereas 238/249 (95%) patients had minimal discomfort. FS in two (1%) patients had to be discontinued because of discomfort.

Regardless of the type of endoscopist, no complications were reported in all nine published studies on FS (17, 18, 21-23, 28-31).

Two studies compared costs of FS performed by nurses or physicians (23, 30). For this, Wallace et al. (23) included salary, pathology costs, staff support, equipment and supplies, and nonphysician training costs for the comparison. The costs per examination were lower for procedures performed by nonphysicians ($186) than for those performed by physicians ($283). In another study, costs of a nurse-led open-access FS service was estimated at $81 per patient, whereas the costs of a physician-led outpatient referral were $161 per patient (30).

Video capsule endoscopy

Two studies evaluated whether nurses were able to detect lesions on VCE recordings (Table 2) (26, 32). Twenty VCE examinations (26) and 50 VCE examinations (32), respectively, were interpreted by a nurse and, independently, re-reviewed by a gastroenterologist. In the first study (26), the nurse missed two (a small angioectasia and a small bowel erosion) of 27 significant lesions seen by the gastroenterologist, whereas the gastroenterologist missed three lesions seen by the nurse. These three lesions were small red spots thought to be angioectasias. In the second study, there was complete agreement between a nurse and a gastroenterologist for all 12 cases interpreted as normal (32). In the remaining cases, the nurse made 130 selections and the gastroenterologist 99 selections. Complete interobserver agreement was achieved for 93 of 96 (97%) lesions categorized as significant by the gastroenterologist. The nurse missed three lesions in three patients, and the gastroenterologist missed four lesions in three patients. The nurse, however, needed more time to read the VCE examination than the gastroenterologist (mean 100 vs. 59 min).

Costs of interpreting VCE was calculated in one study (32). The costs per examination for the standard procedure (physician-only) were $573, which decreased if the nurse had made preliminary thumbnail selections ($249).

Percutaneous endoscopic gastrostomy

Two studies evaluated the safety of nurse-assisted placement of a PEG catheter (Table 2) (24, 25). The nurse was responsible for cleansing and anesthetizing the abdominal surface, making an incision, introducing a guidewire, delivering the PEG catheter and securing it with the locking device. In both studies, no differences in procedure-related complications, infections around the PEG site, or feeding tube-related problems were observed between nurse-assisted and physician-assisted placement.

Management of gastrointestinal disorders

Nightingale et al. (33) evaluated nurse-directed care in the management of patients with IBD. The main aim of this service was to improve education and support for patients and their family and other healthcare professionals involved in the management of patients with IBD. The involvement of a nurse resulted in a 38% reduction in hospital visits and a 19% reduction in in-hospital stay, compared with a historical control group. The number of patients in remission increased from 63% to 69%. Patient satisfaction improved with regard to information on IBD ($p<0.001$), and advices to prevent illness and to maintain health ($p<0.001$).

Schoenfeld et al. (34) retrospectively studied the effectiveness of nurse-directed care of patients with Barrett's esophagus (BE). By using guidelines, a nurse adjusted antireflux medications, evaluated biopsy reports, determined the interval between surveillance endoscopies, and provided education for patients with BE. In 123 patients, it was found that variation from the guidelines with regard to the interval of surveillance endoscopy and treatment of reflux symptoms was less than 2%. In addition, most patients were satisfied with overall medical care (88%), with the replies to their questions (88%) and with patient education (76%). Half of the patients indicated that overall medical care would not change if a physician replaced the nurse, and 38% of patients preferred the nurse to a physician.

DISCUSSION

The use of diagnostic endoscopy has rapidly increased over he last 5-10 years. This is, among other factors, because of the increased awareness on screening for premalignant disorders of the GI tract, particularly Barrett's esophagus and adenomatous polyps. In addition, the introduction of new endoscopic techniques has resulted in an increased demand on the endoscopic capacity. It is noted, however, that it is difficult to have the manpower for the increased demand for both diagnostic and therapeutic endoscopy. The introduction of nurse-led endoscopy, particularly for diagnostic upper endoscopy and sigmoidoscopy, could be a solution for this shortage.

The findings in the reviewed studies suggest that nurses can well perform some of the tasks and diagnostic procedures previously performed by physicians. This review showed that nurses were able to perform diagnostic upper endoscopy, EUS, and FS, and to interpret VCE examinations in an effective and safe way with results similar to those obtained by physicians (Table 2). In addition, it was found that nurses could actively participate in PEG insertion (24, 25). Nevertheless, it is important to emphasize that the quality of the design and methodology used in most studies was weak. We found only three randomized trials (16-18), the remainder was comparative or noncomparative studies (19-34). If nurse endoscopy is introduced in the endoscopic setting, training is obviously of utmost importance, and nurse endoscopists should follow a training program which is comparable to that of fellows.

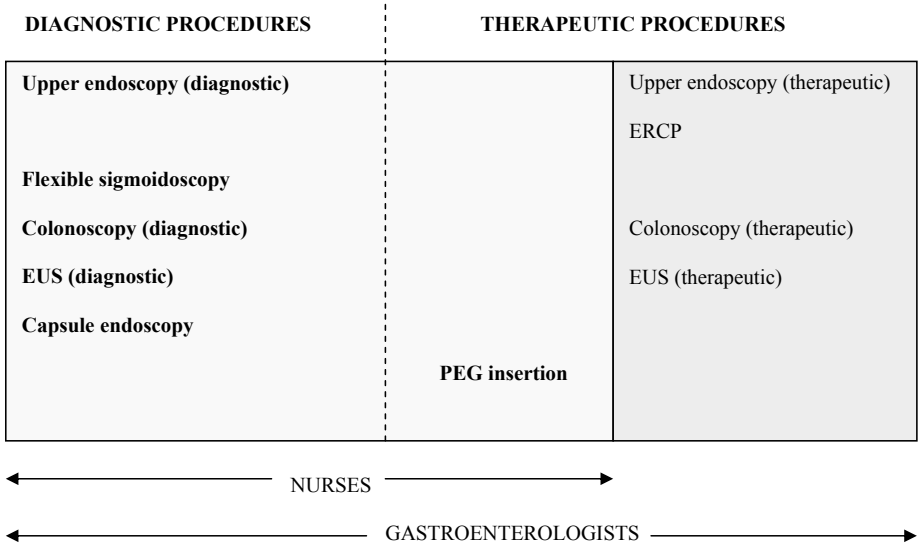

Figure 1. Schematic representation showing which endoscopic procedures could be performed by nurse endoscopists as physician substitutes (highlighted are procedures for which some evidence of its efficacy if performed by nurses has been published)

Professional organizations, such as the Joint Advisory Group on Gastrointestinal Endoscopy in the United Kingdom (35) and the Society of Gastrointestinal Nurses and Associates in the United States (36) have developed guidelines to ensure that nurses are performing endoscopies according to and in line with these guidelines. These guidelines all incorporate recommendations for appropriate training and accreditation in endoscopy, comparable to those for physician trainees. In addition, it is clearly stated in these guidelines that noncompliance would leave nurses vulnerable to medicolegal actions. Guidelines should guarantee that nurses are able to adequately perform diagnostic procedures, such as upper endoscopy for surveillance of Barrett's esophagus or dyspepsia; FS for screening of colorectal cancer; diagnostic colonoscopy for symptoms of hematochezia or surveillance of IBD; diagnostic EUS in the diagnostic workup of esophageal, gastric and pancreatic tumors; and interpreting VCE; and should be involved in some therapeutic procedures e.g. PEG insertion (Figure 1).

Surprisingly, only two studies were identified in which nurses managed patients with specific GI disorders, i.e., IBD and BE (33, 34). It is conceivable that nurses also could be involved in the management of patients with other chronic gastrointestinal disorders, such as chronic pancreatitis and irritable bowel syndrome (37) (Figure 2). If so, clinical guidelines and supervision of physicians are recommended to support nurses in daily practice. In addition, it is important that patients are discussed in regular multidisciplinary meetings. Further studies, however, are needed to evaluate the exact role of nurses in these disorders. In addition, nurses could well play a role in the palliative care of patients with incurable or recurrent

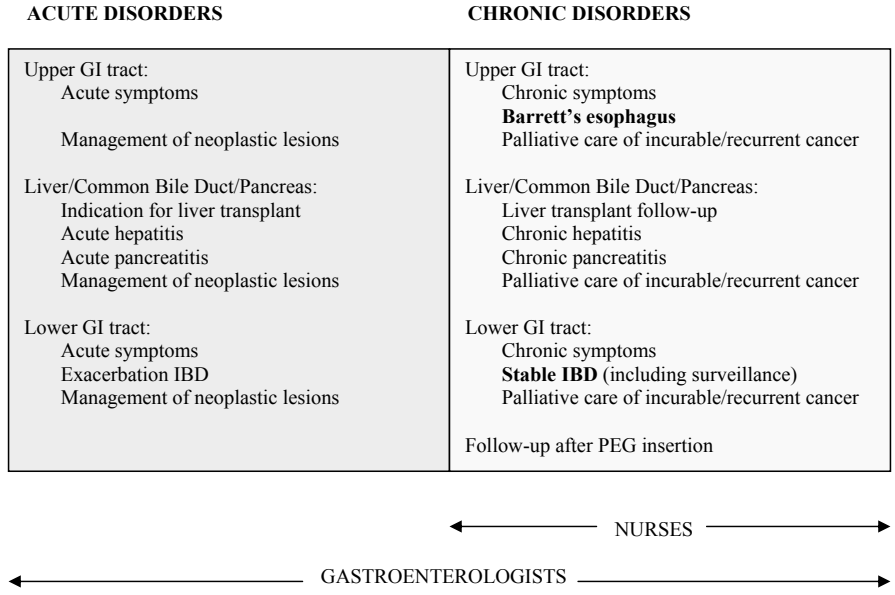

Figure 2. Schematic representation of gastrointestinal (GI) disorders that could be managed by nurses as physician substitutes (highlighted are disorders for which some evidence of its efficacy if performed by nurses has been published).

cancer of the gastrointestinal tract, for example esophageal cancer, gastric cancer, pancreatic cancer (38), or colorectal cancer (39). It is known that nurses increasingly are involved in the care of patients in liver transplant programs (40, 41) and in managing patients undergoing treatment for hepatitis C (42, 43). Finally, the role of the stoma therapist nurse is well established in many centers (39, 44).

Are nurses already widely involved in the gastrointestinal practice? Pathmakanthan et al. (45) investigated the contribution of nurses in endoscopic procedures and the attitude of physicians towards this involvement by mail questionnaire in teaching and district general hospitals throughout the United Kingdom. It was found that 67 of 176 responding hospitals employed 102 nurse endoscopists. Forty-four (43%) of these nurse endoscopists performed both upper endoscopy and FS, with only upper endoscopy and only FS performed by 17 (17%) and 31 (30%) nurses, respectively. Three (3%) nurses performed colonoscopy whereas seven (7%) were involved in all three procedures. Nurse endoscopists were experienced to provide good and safe patient care in the majority of endoscopy units. This, however, was not systematically studied. Lead clinicians stated that they were keen to restrict nurse endoscopy to diagnostic upper endoscopy and FS. Perceived benefits included good patient acceptability, improved care, and safety. Most clinicians predicted an important but still restricted role for nurse endoscopy in the provision of endoscopic services unless efficacy and safety were clearly proven.

Lal et al. (46) performed a postal survey of endoscopic training programs for internal medicine (n=445), family practice (n=471), physician assistants (n=118), and nurse practitioners (n=149) in the United States to evaluate the availability and structure of FS training in these specialities. The overall response rate was 63%. Most internal medicine (89%) and family practice (99%) programs offered FS training versus only 12% of physician assistant and none of nurse practitioner programs. Family practice programs were more likely to offer training ($p<0.001$), require training ($p<0.001$), and teach biopsy techniques ($p<0.001$). Internal medicine programs were more likely to have minimum requirements ($p<0.001$) and required a minimum of 25 procedures per trainee ($p<0.001$). Physician assistant programs were less structured and often lacked minimum requirements. It was concluded that FS training was still restricted or nonexistent among physician assistant and nurse practitioner programs in the United States.

The need for efficient patient education and counseling is growing with the ongoing development of new gastrointestinal and endoscopic technologies (47). Studies show that patient education conducted by nurses may be beneficial to ensure compliance and cost-effectiveness (48, 49). In a study investigating a pre-endoscopy patient education program, it was found that patient education before endoscopic procedures was able to reduce the rate of examination failures and their attending costs (48). In addition, optimal information to patients may benefit patient satisfaction and decrease anxiety.

As a result of technological advances, changes in work practices and instrument processing procedures, contemporary endoscopy services have increasingly become expensive to maintain (50). The introduction of nurse endoscopy could lead to significant cost savings. We found only three studies in which the costs of FS (23, 30) and the interpretation of VCE examinations (32) if performed by nurses were evaluated. This low number was somewhat unexpected in the light of the widely held view that nurse-led care may generate cost savings.

In conclusion, the findings of this review supported the involvement of nurses in different types of gastrointestinal care and diagnostic endoscopic procedures (Figure 1 + 2). In the majority of reviewed studies, nurses worked as physician substitutes. It, however, is important to realize that, so far, only three randomized studies have been published in which the performance of nurses and physicians in GI endoscopy were compared. Therefore, little solid evidence is presently available to definitely conclude that the involvement of nurses in the gastroenterology and endoscopy setting is of benefit to all parties involved, i.e., patients, gastroenterologists and society. More randomized trials need to objectively demonstrate that nurses' performance of gastrointestinal tasks and endoscopic procedures compare at least favorably with physicians in terms of medical outcomes (accuracy and safety), patient satisfaction and costs.

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4

Nurse-led care after esophageal cancer surgery

4A

Experiences and expectations of patients after oesophageal cancer surgery: an explorative study

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ABSTRACT

We investigated which problems patients experience after a resection for oesophageal cancer and what care they expect, in order to devise a better tailored follow-up policy.

Thirty patients, all within one year after surgery, filled in a one-time questionnaire on experienced physical, psychological and social problems and on expected care for these problems. Additionally, a semi-structured interview was performed. Frequencies of experienced problems and expected care over time were analyzed.

The majority of patients experienced physical problems such as 'early satiety' (97%) and 'fatigue' (84%) as problematic after oesophagectomy. In addition, patients often felt depressed (64%), were afraid of metastases (80%) and death (47%). Over time, the frequency of problems such as 'fatigue' ($p=0.035$) and 'being dependent' ($p=0.012$) decreased. Patients particularly expected professional care for physical issues related to their disease, whereas they often managed psychosocial problems in their own social network. Patients indicated that nurses' involvement during follow-up might improve their possibility to satisfactorily deal with problems.

Patients frequently experience physical problems after oesophagectomy, and professional care is expected for these issues. Psychosocial problems are also present but care is less commonly expected. Nurses' involvement during follow-up could be a way to optimize patients' management after oesophageal cancer surgery.

INTRODUCTION

Approximately 400,000 patients per year are world-wide diagnosed with oesophageal cancer, which makes this malignancy the eight most common cancer (1). The incidence of oesophageal cancer has risen remarkably over the past two decades in the Western world, due to a marked increase in the incidence of adenocarcinoma (2, 3).

Surgery for oesophageal cancer is a serious life-event, which may be accompanied by significant morbidity that may influence quality of life of patients (4-12). Common postoperative symptoms include dysphagia, weight loss and a change in eating patterns. In addition, fatigue, reflux symptoms, dumping syndrome, as well as physical limitations in normal daily life are observed, particularly in the first year after an oesophageal resection (5, 7, 10). Treatment and counselling for these physical problems are important issues during follow up after surgery for oesophageal cancer. Psychological and social problems are less frequently discussed, although complications and symptoms after surgery likely influence patients' psychosocial functioning. Recently, psychosocial problems have been acknowledged as an important surgical outcome measure (13-15). It is well known that the majority of patients are concerned that they will develop recurrent cancer after an oesophageal resection (16). Therefore, it is important that questions about treatment and disease related symptoms, and about the prognosis are adequately discussed. Besides, patients may need reassurance and emotional support during follow-up visits (16, 17). However, it is unclear whether patients expect professional help and advice for these problems.

The purpose of this study was to identify and explore the experienced problems, either physical or psychosocial, after oesophageal resection. In addition, patients were asked whether they expected professional help and advice for these problems. This study should give a basis for improvement of our follow-up policy of patients after oesophageal cancer surgery.

MATERIALS AND METHODS

Design and patients

A cross-sectional study design was used. Between July and October 2003, questionnaires were sent to 32 consecutive patients who had undergone an oesophageal resection for carcinoma of the oesophagus or gastric cardia at the Erasmus MC Rotterdam, the Netherlands. Inclusion criteria were: 1) patients had undergone surgery for oesophageal cancer, 2) the time interval between operation and study participation was less than 1 year, and 3) patients were able to understand the Dutch language. Thirty patients filled in the questionnaire and, additionally, a semi-structured interview was performed. The study was approved by the Institutional Review Board of the Erasmus MC Rotterdam.

Data collection

Questionnaire. Data was collected by a self-administered questionnaire, based on the Patients Needs in Palliative Care-checklist (PNPC-checklist) which was originally developed by Osse (18, 19). The questionnaire was modified to assess the problems which patients experience after oesophageal resection for malignancy and the type of care that they expected for these problems. A panel of three experts (a gastrointestinal surgeon, a gastroenterologist and a medical oncologist) had established the face validity of the questionnaire. These experts were asked to judge the questionnaire on relevance and completeness of the items. Prior to inclusion, a pilot study was undertaken involving 3 patients.

The questionnaire comprised 93 items distributed over nine dimensions focusing on activities of daily living, social activities, physical problems, loss of independence, social issues, professional care providers, and psychological, spiritual and information issues (see Appendix). The patients were asked to relate their answers to their present situation, which is at the time of filling in the questionnaire. Answers related to experienced problems could be rated as being frequently problematic, moderately frequent problematic or never problematic. In addition, every dimension ended with an other category where patients could report extra information. Expected care could be rated as more than current care, equal to current care, or no care. In addition, patients were asked to rate their current overall health status on the EuroQol visual analogue scale (VAS) (20), a scale from 0 (the worst possible health state) to 100 (the best possible health state).

Interview. All patients were interviewed personally, one week after filling in the questionnaire, for additional information. The interviews were semi-structured, addressing experienced problems and expected care in more detail. The questions were open questions and related to the nine dimensions of the questionnaire. During the interview, possible nurses' involvement in a future follow-up policy was also discussed.

Statistical analysis

Descriptive statistics included frequencies of experienced problems and expected care. Problems were considered present if they were rated as frequently problematic or moderately frequent problematic and expected care was considered present if this was rated as more then current or equal to current. Chi-square tests were performed to examine the association between experienced problems and expected care on the one hand, and having undergone neo-adjuvant therapy or post-operative dilation of anastomotic strictures on the other hand. Time after surgery was categorized as 1-3, 4-6, 7-9, and 10-12 months for descriptive purposes. Time was used as a continuous variable in Spearman's rank correlation and logistic regression analyses to evaluate the relationship between the time after surgery and experienced problems and expected care. A p-value <0.05 was considered statistically significant. Analyses were conducted using SPSS version 10.1 (SPSS Inc., Chicago, IL., USA) and S-plus version 6.0 (Insightful Inc, Seattle WA, USA).

RESULTS

Clinical characteristics

Thirty patients (mean age: 62 yrs) filled in a questionnaire at a median time of 6 (range: 3-12) months after oesophageal resection followed by a gastric pull-up reconstruction (Table 1). All were disease-free at the time of filling in the questionnaire. Adenocarcinoma was removed in 19 patients, squamous cell carcinoma in 10, and 1 patient had had high-grade dysplasia in Barrett's oesophagus. Fifteen (50%) patients had received neo-adjuvant treatment, consisting of cisplatin and paclitaxel chemotherapy (n=7 [23%]), or a combination of concurrent chemotherapy (carboplatin/paclitaxel) and radiation therapy (41.4 Gy in 23 fractions; n=8 [27%]). Nine patients (30%) had undergone a median of 5 (range: 2-12) dilations for anastomotic strictures. These characteristics were equally distributed across patients who answered the questionnaire early or late during follow-up.

Experiences after surgery

Physical items were most commonly experienced as being problematic (Table 2). Of these, early satiety (n=29 [97%]), eating problems (n=27 [90%]), fatigue (n=25 [84%]), constipation/diarrhoea (n=23 [77%]), pain (n=17 [57%]) and loss of weight (n=13 [44%]) were most frequently noted as being problematic (Table 2, Figures 1a-1b). During the interviews, patients indicated that difficulties with eating, changes in bowel habits and fatigue had a negative impact on their efforts to resume or perform social activities. The majority of patients (n=21

Table 1. Clinical characteristics of 30 patients after surgery for oesophageal cancer

Gender (M/F)	21/9
Age in years; mean (sd)	62 (11)
Time between surgery and interview; no. of patients	
1-3 months	6
4-6 months	9
7-9 months	6
10-12 months	9
Tumor histology; no. of patients	
Adeno carcinoma	19
Squamouscell carcinoma	10
High-grade dysplasia	1
Neo-adjuvant therapy; no. of patients)	
Chemotherapy	7
Chemo-radiation	8
None	15
Dilation after surgery, before date of interview; no. of patients	
0-2	24
≥ 3	6

Table 2. The most frequently experienced problems of 30 patients after surgery for oesophageal cancer and the care patients expect from professionals

	Experienced problems; no. of patients (%)		Expected care; no. of patients (%)
	Often	**Sometimes**	**More or equal**
Physical problems			
Early satiety after meal	14 (47)	15 (50)	20 (67)
Eating	7 (23)	20 (67)	20 (67)
Constipation or diarrhoea	8 (27)	15 (50)	18 (60)
Fatigue	11 (37)	14 (47)	15 (50)
Pain	5 (17)	12 (40)	15 (50)
Loss of weight	8 (27)	5 (17)	12 (40)
Psychological problems			
Fear for metastases	6 (20)	18 (60)	19 (63)
Fear for physical suffering	3 (10)	13 (44)	13 (44)
Fear for death	0 (0)	14 (47)	15 (50)
Depressed mood	2 (7)	17 (57)	12 (40)
Unpredictability of the future	2 (7)	16 (53)	14 (47)
Frustration not managing as usual	5 (17)	9 (30)	12 (40)
Social problems			
Continuing the usual activities	4 (13)	16 (53)	11 (37)
Giving away tasks	7 (23)	10 (33)	12 (40)
Being dependent	6 (20)	9 (30)	11 (37)
Others being over-concerned	4 (13)	11 (37)	10 (33)

[70%]) reported that the once-only dietary consultation during hospitalization had not been helpful in their daily home situation. The main reasons were that patients were not advised to follow strict dietary rules and that patients had to explore themselves what type of food they were able to eat. The longer after surgery, the fewer patients rated symptoms of fatigue (6/6 patients [100%] at 1-3 months vs. 5/9 patients [56%] at 10-12 months, p=0.035) and loss of weight (4/6 patients [67%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.035) as being problematic (Figures 1a-1b). During the interviews, patients indicated that fatigue was most prominent during the first 6 months after surgery. Seventeen (57%) patients had experienced symptoms of pain (Table 2), most commonly in the chest/upper abdomen or headache.

Fear for metastases (n=24 [80%]) was the most commonly experienced psychological problem (Table 2, Figures 2a-2b). Many patients felt depressed at times (n=19 [64%]), and were afraid of physical suffering (n=16 [53%]) or death (n=14 [47%]), and more than half of the patients indicated the unpredictability of the future as being problematic (Table 2). Over time, fewer patients indicated that they were afraid for these events. However, the differences over time were not statistically significant (Figure 2a-2b). The longer after surgery, the fewer patients indicated that they felt frustrated, being unable to resume daily matters as they did

previously (5/6 patients [83%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.034). In addition, they also experienced more pleasure in life (4/6 patients [67%] at 1-3 months vs. 1/9 patients [11%] at 10-12 months, p=0.050) and had fewer difficulties in showing their emotions to family and friends (4/6 patients [67%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.048) (Figures 2a-2b).

Social problems were present but less prominent (Table 2). The longer the time after surgery, the less frequently patients recorded that they felt dependent (6/6 patients [100%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.012) or experienced that others were concerned about their well-being (4/6 patients [67%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.042). Patients noticed that they were able to pick up their usual day-by-day activities over time so that they no longer had to leave several activities to others (5/6 patients [83%] at 1-3 months vs. 3/9 patients [33%] at 10-12 months, p=0.028).

As far as contact with medical and non-medical professionals was concerned, patients were increasingly able to remember the information that was given (6/6 patients [100%] at 1-3 months vs. 4/9 patients [44%] at 10-12 months, p=0.035), experienced less hesitation in asking for help and advice (4/6 patients [56%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.034), or for additional information about their disease and what to expect in the future (3/6 patients [50%] at 1-3 months vs. 1/9 patients [11%] at 10-12 months, p=0.047). During the interview, patients indicated that these issues were important, particularly in the first 6 months after surgery. The main reason for this was that patients were uncertain about their prognosis and additional treatment options, and that they felt dependent on medical professionals. In addition, patients initially experienced a lack of concentration during follow-up visits.

When asked to rate their current overall health status, patients scored a mean value of 70 (range: 20-93) on a scale from 0 to 100. Over time, a slight improvement of the overall health status was observed. In the first three months after oesophageal resection, patients rated their overall health status with a mean value of 59 (range: 20-80) whereas 10-12 months after surgery a mean value of 72 (range 20-90) was scored (p=0.029).

Patients with three or more post-operative dilations for anastomotic structures (n=6) had significantly more difficulties with swallowing (p=0.049) than patients with fewer or no dilations. Patients who had received neo-adjuvant therapy (n=15) had the impression of 'lost body control' less frequently (p=0.025) and had fewer problems with decision-making (p=0.027). No association was found between the administration of neo-adjuvant therapy and experienced physical problems and expected care.

Expected care

The majority of the patients experienced difficulties with eating and changes in bowel habits, and they also expected care and attention from medical and non-medical professionals for these problems (Table 2, Figures 1c-1d). Although the inability to eat normal food was an

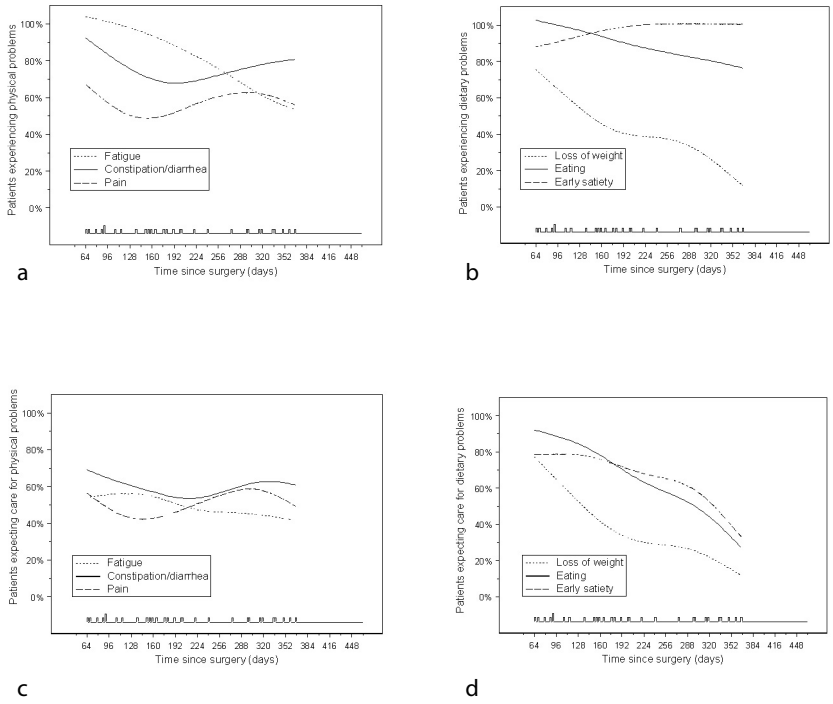

Figure 1. The physical problems 'fatigue', 'constipation/diarrhoea' and 'pain' (A) and 'weight loss', 'early satiety' and 'eating problems' (B), experienced by 30 patients at different points in time after surgery for oesophageal cancer, and the expected care for these problems (C and D)

important issue in the majority of patients, only 3 (10%) patients visited a dietician during follow-up, whereas another two (7%) had the intention to do so. Over time, the frequencies of expectations of professional care for physical problems such as difficulties with eating (5/6 patients [8%] at 1-3 months vs. 4/9 patients [44%] at 10-12 months, p=0.029), loss of weight (4/6 patients [67%] at 1-3 months vs. 2/9 patients [22%] at 10-12 months, p=0.05) and early satiety (4/6 patients [67%] at 1-3 months vs. 4/9 patients [44%] at 10-12 months, p=0.10) declined (Figures 1d). Although still a burden, most patients reported that they more or less had accepted these difficulties.

If patients experienced difficulties, this did not always mean that they expected professional care for these problems. On the other hand, patients sometimes expected attention for a non-existing problem, just in case that specific problem would occur in the future (Table 2).

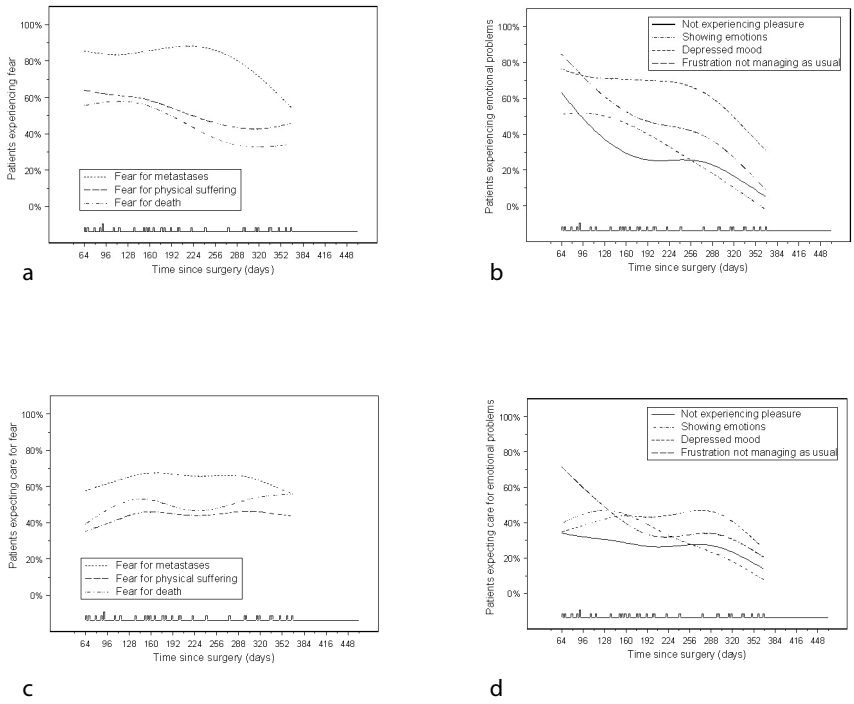

Figure 2. The psychological problems 'fear for metastases', 'fear for physical suffering' and 'fear for death' (A) and 'not experiencing pleasure', 'showing emotions' 'depressed mood' and 'frustration not managing as usual' (B), experienced by 30 patients at different points in time after surgery for oesophageal cancer, and the expected care for these problems (C and D)

It was not easy for patients to explain why specific problems resulted in an experienced need for care. In cases where professional care for psychosocial problems was expected, patients most often indicated that support in dealing with their disease was needed (Table 2). In addition, patients expected information about physical problems which they could develop in the future (n=27 [90%]), treatment options and side effects (n=26 [87%]), diet (n=25 [83%]) and causes of cancer (n=24 [80%]).

None of the patients had consulted a psychologist or social worker, and only three (10%) patients indicated that they had the intention to do so. The majority of patients indicated that support from family and friends was sufficient, particularly for psychological and social issues.

During the interviews, the possible role of specialized nurses in a future follow-up policy was discussed. The majority of the patients (n=24 [80%]) would appreciate involvement of

nurses during follow-up, whereas only 4 patients (13%) had reservations. Two patients (7%) had no opinion. The main reason that patients supported involvement of nurses during follow-up was that patients expected that it was easier to discuss problems with nurses. In addition, patients indicated that they sometimes had to wait for a long time to consult a doctor and that not always the same doctor could be consulted during follow-up. They expected that the involvement of nurses during follow-up after oesophageal resection might improve the continuity of care.

DISCUSSION

Although patients generally had several psychological and social problems, physical problems were the most commonly experienced after surgery for oesophageal or gastric cardia cancer. In particular, issues related to food intake, fatigue and defecation problems, such as diarrhoea or constipation, were recorded by the majority of patients as being problematic (Table 2). This is in line with findings in other studies, in which different combinations of these issues were reported as being problematic, even in long-term survivors (5-11).

With regard to the experienced psychological problems, particularly a depressed mood, fear for metastases, physical suffering and death were the most commonly reported (Table 2). In the past decade, there has been an increasing awareness of the psychological responses to a diagnosis of cancer, particularly with regard to the occurrence of emotional distress, anxiety, and a depressed mood (21). Blazeby et al. (4) and Bernhard et al. (16) reported that mainly physical problems had a negative impact on quality of life. In contrast, others found that patients may have a satisfactory life even with physical limitations after surgery for oesophageal cancer (6, 9-12). Although we did not specifically examine quality of life after surgery, patients scored a mean of 70 (on a scale from 0 to 100) for evaluation of their own health, despite the experienced physical problems. Since the overall prognosis for oesophageal cancer is dismal with a 5-year survival rate around 20% (22), it seems likely that patients are willing to accept some physical limitations after surgery. In addition, it is conceivable that the longer disease free, the higher the score on the overall health status will be.

Over time, we found that several physical, psychological and social problems were less prominent (Table 2, Figures 1 and 2). This is in accordance with findings by Zieren et al. (7), who reported that role and physical functioning had improved 6-9 months after an oesophageal resection. At 12 months after surgery, symptoms such as fatigue and loss of weight were also rated as less prominent than before the operation. It became clear during the interviews that support from family and friends or sufficient care and advice of medical and non-medical professionals might have positively influenced the burden of symptoms in this group of patients.

Not surprisingly, an association was found between dilations for post-operative anastomotic strictures and problems with swallowing (p= 0.049). It has been shown that dysphagia and problems with swallowing are postoperative symptoms that may persist in patients after oesophagectomy for a prolonged period (6, 9-12). We found no association between the administration of neo-adjuvant therapy and experienced physical problems. However, the 15 patients who underwent neo-adjuvant therapy had the impression of lost body control less frequently (p=0.025) and experienced fewer problems with decision-making (p=0.027). In contrast, Brooks et al. (5) found that patients receiving surgery alone experienced a higher health-related quality of life and less mood disorders during the postoperative period, compared with those who had also received neo-adjuvant therapy. We speculate that our patients might have been more aware of symptoms experienced after treatment with neo-adjuvant therapy, so that surgery was less burdening to them. In addition, these patients undergo intensive follow-up by physicians and social workers during treatment with neo-adjuvant therapy, which may have influenced their attitude towards physical problems. Besides, because of the intensive follow-up during neo-adjuvant treatment, it seems likely that these patients had more access to professional support that could address their problems.

In accordance with our findings, it has been reported that interventions by medical and non-medical professionals are most often indicated when experienced problems interfere with functioning (23). Although it can be expected that cancer patients with psychological problems may perceive benefit from individual psychological support, they often are reluctant to indicate that they are anxious or depressed (17, 24-26). Patients may not want to burden professional caregivers or, probably more likely, they feel there is still a stigma associated with mental or psychological issues in relation to disease (21). In addition, most physicians mainly focus on obtaining objective physical data and they sometimes have difficulty in dealing with subjective psychological and social problems of patients (13). As suggested during the interviews, involvement of nurses during follow-up after surgery for oesophageal cancer could be beneficial to patients. Recently, there has been a tendency towards more nurse-led oncological care (27). It has been shown that nurse-led follow-up of outpatients may improve quality of life (28-31). Besides, it has been suggested that a nurse-led service may lead to a net cost reduction (29, 30).

A limitation of this study is that only 30 patients filled in questionnaires at one time point after oesophageal cancer surgery. In order to more precisely investigate the course of physical, psychological and social problems that patients experience after surgery for oesophageal cancer over time, further longitudinal research is needed. As this study was designed as an explorative study, the outcome will be used to evolve our follow-up policy of patients after oesophageal cancer surgery. Currently, we are performing a randomized trial to evaluate the effects of nurses' involvement during follow-up on quality of life and costs after a resection for oesophageal cancer.

In conclusion, patients frequently experience physical problems after oesophagectomy, and professional care is expected for these issues. Psychosocial problems are also present but care is less commonly expected. Nurses' involvement during follow-up could be a way to optimize patients' management after oesophageal cancer surgery.

ACKNOWLEDGEMENT

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APPENDIX

Questionnaire

General questions

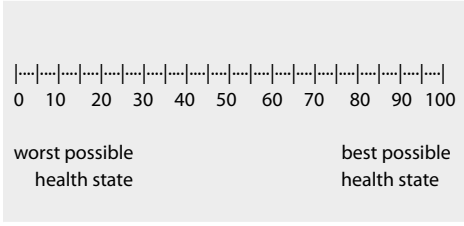
What is your date of birth? …….. / ……. / …… (day / month / year)

What is your sex?
○ male
○ female

What is your marital state?
○ married or living with a partner
○ widow or widower
○ divorced
○ single
○ other, ……

When did you undergo your operation?…….. / ……. / …… (day / month / year)

How would you rate your over-all health status at this moment?
"100" means the best possible health state, and "0" means the worst possible health state.
Please mark the point on the scale that you feel best illustrates your current health state.



Specific questions

Activities of daily living						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Body care, washing, dressing or toilet	○	○	○
○	○	○	Walking, climbing stairs	○	○	○
○	○	○	Preparing meals or cooking	○	○	○
○	○	○	Shopping (food, clothes, etc.)	○	○	○
○	○	○	Personal transportation	○	○	○
○	○	○	Light household work	○	○	○
○	○	○	Heavy household work	○	○	○

Social activities						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Filling up the day	○	○	○
○	○	○	Relaxing	○	○	○
○	○	○	Doing work or studying	○	○	○
○	○	○	Continuing usual activities	○	○	○
○	○	○	Caring for children or baby sitting	○	○	○
○	○	○	Continuing social activities	○	○	○

Physical problems						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Difficulties with eating	○	○	○
○	○	○	Difficulties with drinking	○	○	○
○	○	○	Swallowing problems	○	○	○
○	○	○	Early satiety	○	○	○
○	○	○	Nausea and/or vomiting	○	○	○
○	○	○	Dry mouth	○	○	○
○	○	○	Change of taste	○	○	○
○	○	○	Coughing	○	○	○
○	○	○	Belching	○	○	○
○	○	○	Heartburn	○	○	○
○	○	○	Pain	○	○	○
○	○	○	Weight loss	○	○	○
○	○	○	Fatigue	○	○	○
○	○	○	Difficulties with sleeping	○	○	○
○	○	○	Constipation/diarrhoea	○	○	○

Loss of independence						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Others being over-concerned	○	○	○
○	○	○	Being alone	○	○	○
○	○	○	Difficulties with giving away tasks	○	○	○
○	○	○	Being dependent on others	○	○	○
○	○	○	Frustration because of being not able to manage usual daily affairs	○	○	○
○	○	○	Feeling of losing control on your own life	○	○	○

Social issues						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Relationship with partner	○	○	○
○	○	○	Talking about disease with partner	○	○	○
○	○	○	Contact with (one of) the children	○	○	○
○	○	○	Contact with family, friends, neighbours	○	○	○
○	○	○	Finding it difficult to talk about disease, because of not willing to burden others	○	○	○
○	○	○	Finding others not receptive in talking about the disease	○	○	○
○	○	○	Experiencing too little support of others	○	○	○
○	○	○	Difficulties in finding someone to share private thoughts with	○	○	○
○	○	○	Receiving too little help from life companion or family	○	○	○
○	○	○	Others making the situation more dramatic	○	○	○
○	○	○	Others denying the seriousness of the situation	○	○	○
○	○	○	Being afraid to be left alone	○	○	○

Professional caregivers						
Is this a problem?				*Do you expect help?*		
Often	Sometimes	Never		Yes, more than currently	Equal to currently	No
○	○	○	Asking for help	○	○	○
○	○	○	Making own decisions	○	○	○
○	○	○	Expressing disagreement	○	○	○
○	○	○	Indicating you don't understand what was said to you	○	○	○
○	○	○	Remembering what was said to you	○	○	○
○	○	○	Asking questions	○	○	○

At this moment, do you receive professional care from one of the caregivers, as stated below? (more than one answer is allowed)

○ general practitioner
○ surgeon
○ nurse
○ home help
○ social worker
○ psychologist
○ other, ……

Do you need (more) professional care from one of the caregivers, as stated below? (more than one answer is allowed)

○ general practitioner
○ surgeon
○ nurse
○ home help
○ social worker
○ psychologist
○ other, ……

Psychological issues						
Is this a problem?				*Do you expect care?*		
Often	Less often	Never		Yes, more than currently	Equal to currently	No
○	○	○	Depressed mood	○	○	○
○	○	○	Not experiencing pleasure anymore	○	○	○
○	○	○	Fear for physical suffering	○	○	○
○	○	○	Fear for treatment	○	○	○
○	○	○	Fear for metastases	○	○	○
○	○	○	Fear to be alone	○	○	○
○	○	○	Fear for death	○	○	○
○	○	○	Coping with the unpredictability of the future	○	○	○
○	○	○	Difficulties to show emotions	○	○	○
○	○	○	Feelings of guilt	○	○	○
○	○	○	Feelings of shame	○	○	○
○	○	○	Losing control of emotions	○	○	○
○	○	○	Accepting a change in body appearance	○	○	○
○	○	○	Being optimistic about the future	○	○	○
○	○	○	Experiencing loss of control over own body	○	○	○
○	○	○	Being overwhelmed by all the decisions that have to be made	○	○	○

Spiritual issues						
Is this a problem?				*Do you expect care?*		
Often	Less often	Never		Yes, more than currently	Equal to currently	No
○	○	○	Being meaningfully engaged	○	○	○
○	○	○	Being of importance to others	○	○	○
○	○	○	Continuing belief in God or religion	○	○	○
○	○	○	Being concerned about the meaning of death	○	○	○
○	○	○	Accepting the disease	○	○	○

Information issues		
	Do you rate this issue as important?	
	Yes	No
Information about available aids (alarm devices, adaptations to the home, etc.)	○	○
Information about places and agencies that provide help	○	○
Information about causes of cancer	○	○
Information about treatment options and side effects	○	○
Information about physical problems that can be expected	○	○
Information about alternative healing methods	○	○
Information about euthanasia	○	○
Information about diet	○	○
Information about sexuality of patients treated for cancer	○	○

4B

Nurse-led Follow-up of Patients after Oesophageal Cancer Surgery: a Randomised Trial

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Submitted

ABSTRACT

Background: A surgical resection for oesophageal cancer is accompanied by significant morbidity and impact on the quality of life of patients. Disease-related symptoms and questions of patient regarding prognosis should be adequately addressed during follow-up visits.

Methods: Between January 2004 and February 2006, 109 patients were randomised to standard follow-up at the outpatient clinic (usual follow-up; n=55) or by regular home visits performed by a specialist nurse (nurse-led follow-up; n=54) 6 weeks, and 3, 6, 9 and 12 months after randomisation. Longitudinal data on generic (EORTC QLQ-C30, EQ-5D) and disease-specific quality of life (EORTC QLQ-OES18), patient satisfaction, medical outcome and costs were collected at randomisation 6 weeks postoperatively and 4, 7 and 13 months afterwards. Differences in outcome over time were assessed by analysis of covariance, chi-square tests, Mann-Whitney tests and cost effectiveness acceptability curves.

Results: A statistically significant and clinically relevant improvement in the eating scale (EORTC QLQ-OES18), and in the fatigue, physical, role and social functioning scales and in global health (EORTC QLQ-C30) were observed in all patients during follow-up. We found no significant differences in quality of life scores between the two follow-up groups over time. In addition, no differences were found in patient satisfaction between the two groups (p=0.14), although spouses were more satisfied with nurse-led follow-up (p=0.03). In total, 11 (20%) patients in the nurse-led follow-up group and 16 (29%) patients in the usual follow-up group developed metastases at a median of 8 months after randomisation (p=0.50). Mean hospital stay was 8.9 in the nurse-led follow-up group versus 17.8 days in those undergoing usual follow-up (p=0.07). Total medical costs, including cost of follow-up, intramural care, diagnostic procedures, additional treatments and extramural care, were lower for nurse-led follow-up (€2,600 vs. €3,800), however, due to the large variation this was not statistically significant (p=0.11). A cost effectiveness acceptability curve indicated, however, that nurse-led follow-up compared with usual follow-up was associated with a 91% chance of leading to significant cost savings.

Conclusions: Patients after curative oesophageal cancer surgery can safely be followed up by a specialist nurse. This alternative follow-up seems less costly compared to usual care and does not adversely affect quality of life, patient satisfaction and medical outcome.

INTRODUCTION

Approximately 400,000 patients per year are worldwide diagnosed with oesophageal cancer, which makes this malignancy the eight most common cancer (1). The incidence of oesophageal cancer has risen remarkably over the past two decades in the Western world, due to a marked increase in the incidence of adenocarcinoma (2, 3). Despite recent advances in the curative treatment of oesophageal cancer (4), less than 50% of patients have operable disease at presentation.

Surgery for oesophageal cancer is a serious life-event, which is often accompanied by significant morbidity and, obviously, will influence quality of life of patients (5-12). It has been reported that approximately 30% of patients will develop recurrent cancer within the first year after oesophageal resection (13). For these patients, the prognosis is dismal and palliation of symptoms is usually the only treatment option. Counselling and treatment of physical problems are therefore important issues during follow-up. Recently, psychosocial problems have been acknowledged as a main surgical outcome measure (14). It is important that questions about treatment, disease-related symptoms and prognosis are adequately discussed. In addition, patients may need reassurance and emotional support during follow-up visits (15, 16).

Over the last few years, the role of nurses in healthcare has been expanding (17). As previously, nurses are providing services which complement or extend those provided by physicians. Recently, nurses have increasingly become involved in tasks and procedures previously performed by physicians (18, 19). One area of nurses' involvement in advanced care is the development of nurse-led services in cancer care (20, 21). Recently, we performed a randomised trial (the SIREC study), in which 209 patients were randomised to single dose (12 Gray) brachytherapy or stent placement (22). In this study, patients were prospectively followed by home visits by specialized research nurses. These specifically trained nurses assisted patients with filling out questionnaires on quality of life, and they were found to be important in giving advice and support to these patients. Based on this experience, we proposed that home visits by specialized nurses could be an alternative to regular controls performed by physicians at the outpatient clinic for patients who have undergone surgical treatment for oesophageal cancer.

In the present study, patients after intentionally curative surgery for oesophageal cancer were randomised to follow-up at the outpatient clinic or to follow-up by regular home visits carried out by a specialist nurse. We aimed to compare these two follow-up groups with respect to health-related quality of life, medical outcome, patient satisfaction and costs (23).

METHODS

Study population

Between January 2004 and February 2006, 120 consecutive patients with intentionally resectable oesophageal carcinoma were eligible to enter the trial. Since 11 patients refused to participate, 109 patients were randomised to standard follow-up by surgeons at the outpatient clinic (usual follow-up, n=55) or regular home visits carried out by a specialized nurse (nurse-led follow-up, n=54) (Figure 1). The major reason for not willing to participate was a preference for follow-up by a physician (n=9). Two patients indicated that study participation was too much of a psychological burden. Inclusion criteria included surgery with curative intent for oesophageal or gastric cardia cancer and a written informed consent. Patients were excluded if they were admitted to a nursing home after hospital discharge or if they had insufficient knowledge of the Dutch language.

The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands. Participating centres included one university hospital (Erasmus MC - University Medical Centre Rotterdam; n=105), and one general hospital (Reinier de Graaf Hospital Delft; n=4).

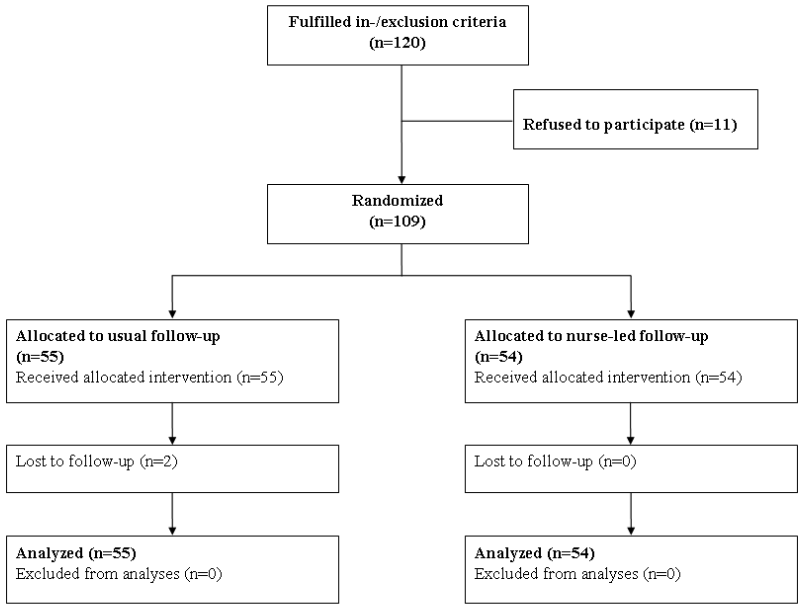

Figure 1. Flow chart of the study comparing usual follow-up with nurse-led follow-up in 109 patients after oesophageal cancer surgery

For randomisation, patients were stratified for radiation and/or chemotherapy prior to surgery, and hospital. Randomisation was performed centrally by the Trial Office of the Department of Oncology, Erasmus MC Rotterdam, using a computer-generated allocation protocol.

Interventions

Three weeks after hospital discharge, all patients visited the outpatient clinic for the first follow-up visit. After informed consent, patients were randomised to usual follow-up or nurse-led follow-up. Nurse-led follow-up was carried out by home visits of a specialist nurse with more than 10 years experience in oncological care. A protocol was developed including nursing diagnosis and interventions, guidelines and decision points, preconditions, and medical-legal consequences. Didactic training included a syllabus on diagnosis and treatment of oesophageal carcinoma and potential problems after oesophageal resection. During follow-up, all patients were discussed in 4-weekly multidisciplinary meetings.

The usual follow-up was performed by a group of 3 senior surgeons at the outpatient clinic of the Erasmus MC Rotterdam and Reinier de Graaf Hospital Delft. In both patient groups, follow-up was performed 6 weeks, and 3, 6, 9 and 12 months after randomisation.

Study endpoints

The primary outcome of the study was health-related quality of life (HRQoL); secondary outcomes included patient satisfaction, medical outcome (dysphagia score, WHO performance score, physical problems), survival and costs.

HRQoL was assessed using the oesophageal cancer specific European Organization for Research and Treatment of Cancer (EORTC) QLQ-OES18 measure (24), the generic EORTC QLQ-C30 measure (25), the EuroQol-5D measure (26) including a self-classifier with 5 questions and a visual analogue scale (EQ-VAS) for the measurement of overall self-rated health, and the Hospital Anxiety and Depression Scale (HADS) (27). The EORTC QLQ-OES18 incorporates five multi-item scales (dysphagia, eating, deglutition, indigestion, pain) and four single symptoms scales (having a dry mouth, and troublesome taste, coughing and talking). Answer categories of the questions range from 'not at all' (scored as 1) to 'very much' (scored as 4). The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, nausea/vomiting, pain), and a global health/quality of life scale. Various single symptoms are included as well. The scoring system of the EORTC QLQ-C30 is equivalent to the scoring system of the EORTC QLQ-OES18.

As no specific validated questionnaire was available to assess patient satisfaction in this setting, a satisfaction questionnaire was developed for patients as well as their spouses. Answers related to satisfaction could be rated as being very satisfied, satisfied, dissatisfied, very dissatisfied. Response was considered positive if answers were rated as very satisfied or satisfied, and response was considered negative if answers were rated as dissatisfied or very

dissatisfied. A panel of three experts (a methodologist, a gastroenterologist and a gastrointestinal surgeon) had established the face validity of the questionnaires. Prior to its use in this trial, the questionnaire was tried out in 5 patients.

Costs that were evaluated included those of follow-up, intramural care, diagnostic procedures, additional treatments (for example palliative treatment) and extramural care. 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 the microcosting method (28). All costs are reported in Euro for the year 2006.

Data collection

HRQoL questionnaires were completed at randomisation (at the outpatient clinic), and 4, 7 and 13 months after randomisation (postal mailing). The questionnaire assessing patient satisfaction was filled out 7 months after randomisation. The response rate was >95% for the whole follow-up period. In total, 135/141 (96%) questionnaires in the usual follow-up group and 144/147 (98%) in the nurse-led follow-up group could be analysed. The use of medical services and palliative treatment (if indicated) was assessed during follow-up visits. In addition, the participating surgeons as well as the specialist nurse filled out standardized case record forms during follow-up visits. For each patient, we registered the ability to eat and/or swallow using a dysphagia score (29), graded as: 0 = ability to eat a normal diet; 1 = ability to eat some solids; 2 = ability to eat some semisolids only; 3 = ability to swallow liquids only; 4: complete dysphagia, general health as assessed by the WHO performance score, graded as: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time; 4 = 100% bedridden, and body weight.

Statistics

Analyses were performed on an intention-to-treat basis. We initially calculated that two groups of 50 patients would be sufficient for a difference of approximately 0.56 standard deviation on the standardized EORTC QLQ-OES18 questionnaire, with a two-sided alpha of 5%, and a power of 80%.

We analysed the quality of life scores with analysis of repeated measurements (30). For each scale a model was fitted that estimated levels for all six combinations of time and follow-up group. Time and follow-up group were included as fixed factors; the patient was the random factor. An ANOVA was performed to test for interaction between time and follow-up group and confidence intervals around the six levels were computed based on the model. For the easier interpretation of differences between randomised groups, we also estimated the average differences over time for scales on which no clear interaction was noted ($p>0.10$). Clinical outcome and patient satisfaction were expressed as means ± standard deviation (SD), and medians and interquartile range (IQR); survival was expressed as median survival. Since cost data per patients 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). Uncertainty was further analysed with a cost effectiveness acceptability curve (CEAC), which is able to show the probability that nurse-led follow-up of patients is cost effective compared with outpatient clinic follow-up by a physician for a range of values that a decision maker is willing to pay for per one point gain in the EQ-VAS (32).

A p-value <0.05 was considered statistically significant. Calculations were performed with SPSS version 11.5 (SPSS Inc., Chicago, IL, USA), and S-plus 6.0 (Insightful Inc., Seattle, WA, USA).

RESULTS

Patient demographics

The two patient groups were similar with respect to clinical characteristics (Table 1). Both groups consisted predominantly of males, with a mean age of 61 year. In 84 (77%) patients, a transhiatal oesophagectomy was performed and in 25 (23%) patients a transthoracic oesophagectomy. Postoperative complications at the intensive care unit included predominantly pulmonary complications and anastomotic leakage, which were in 23 (42%) patients in the usual follow-up group and in 22 (41%) patients in the nurse-led follow-up group. The mean postoperative hospital stay was 23 (range 10-86) days, with no differences between both follow-up groups (p= 0.81).

Health-related quality of life

For the disease-specific EORTC QLQ-OES18 measure, there were no overall differences between patients in the usual follow-up group and the nurse-led follow-up group over time (Figure 2). The largest improvement was seen in all patients at 4 months compared to baseline (Table 2). A clinical and significant improvement was found in the dysphagia (Figure 2b), eating, and indigestion scales, whereas the deglutition and pain scales remained stable. At 4 months, the scores on the single items scales had improved significantly compared to baseline and these remained stable after 13 months.

For the generic EORTC QLQ-C30 measure, a clinical and significant improvement at 4 months was found in the fatigue, physical (Figure 2a), role, cognitive and social functioning scales and in global health (Table 2), which remained stable until 13 months. At 4 months, the scores on the single items scales, except for financial difficulties, had improved significantly compared to baseline and these remained stable until 13 months. We found no significant differences in the generic quality of life scores over time between the two follow-up groups. The generic HRQoL of all patients was, however, already lower at baseline compared to a general German population (33). After 13 months, the largest differences between the study group and the reference group were found for nausea/vomiting (+14 points), followed by

Table 1. Clinical characteristics of 109 patients randomised to usual follow-up or nurse-led follow-up after oesophageal cancer surgery

	Usual follow-up n=55	**Nurse-led follow-up n=54**
Mean age; years ± sd	61 ± 7	61 ± 9
Gender; no. of patients (%)		
Male	41 (75)	40 (74)
Female	14 (25)	14 (26)
Surgical technique; no. of patients (%)		
Transhiatal oesophagectomy	41 (75)	43 (80)
Transthoracic oesophagectomy	14 (25)	11 (20)
Type of reconstruction; no. of patients (%)		
Gastric tube interposition	54 (98)	54 (100)
Colon interposition	1 (2)	0 (0)
Tumour histology; no. of patients (%)		
Adenocarcinoma	42 (76)	40 (74)
Squamous cell carcinoma	12 (22)	13 (24)
Other	1 (2)	1 (2)
Prior radiation and/or chemotherapy; no. of patients (%)		
Total	17 (31)	14 (26)
Chemotherapy	12	6
Radiation and chemotherapy	5	8
Mean postoperative hospital stay; days ± sd	23 ± 13	23 ± 16
Pathological staging; no. of patients (%)		
Stage 0 - I	15 (27)	13 (24)
Stage II	19 (34)	12 (22)
Stage III	8 (15)	13 (24)
Stage IV	13 (24)	16 (30)
Median dysphagia score at baseline (IQR)	0 (1)	0 (1)
Median WHO performance score at baseline (IQR)	1 (1)	1 (1)
Weight at baseline; kg; mean ± sd	73 ± 15	75 ± 14

role functioning (-12 points), fatigue (+11 points), cognitive functioning (-7 points), physical functioning (-6 points) and global health status (+6 points) (33). Regarding the single items, the largest differences for these were found for loss of appetite and diarrhoea (+12 points), followed by constipation (+7 points) and dyspnoea (+5points). For the other scales, the differences were less than 5 points.

The scores on the Euroqol, the EQ-5D index and visual analogue scale for overall self-rated health, significantly improved during follow-up, but were not significantly different for both follow-up groups (Figures 2c). At 13 months, no differences were found between the reference group and our study group (34).

The mean score on the HAD scale was for both follow-up groups 5 points on both the anxiety and depression scale, which remained stable during follow-up (Figure 2d). A score

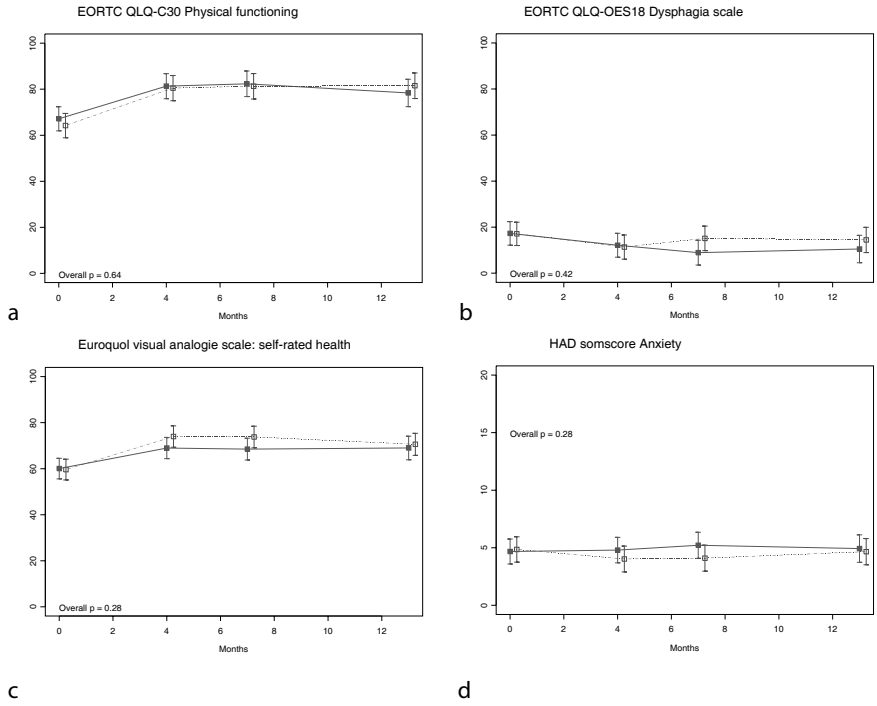

Figure 2. Quality of life scores after usual follow-up (n=55) or nurse-led follow-up (n=54) after oesophageal cancer surgery, including physical functioning (2A) from the EORTC QLQ-C30, the dysphagia scale (2B) from the EORTC QLQ-OES18, the EQ-VAS (2C), and the anxiety scale of the HAD (2D). Graphs show the mean scores with 95% confidence intervals of the different quality of life scales during follow-up. On the physical functioning scale and the EQ-VAS, higher scores represent a better functioning or quality of life. In contrast, higher scores on the dysphagia scale and the HAD scale higher scores represent more dysphagia or anxiety.

above 10 points is often considered to be a cut-off score for anxiety or depression. Therefore, a score of 5 points indicated that the patients were neither anxious nor depressed.

Patient satisfaction

The satisfaction questionnaire was completed seven months after randomisation (response rate 93/98 (95%)). No differences were found for overall patient satisfaction between the two follow-up groups, although spouses of patients in the nurse-led follow-up group were more satisfied with the nurse-led follow-up visits then those in the usual follow-up group (overall rating: 8.1 vs. 7.4; p=0.03) (Table 3). In contrast to their spouses (p=0.05 in advantage

Table 2. Changes in health related quality of life (HRQoL) after 4 months follow-up of patients after oesophageal cancer surgery.

Scale	General population scores*	Mean baseline value (SD)		Changes in HRQoL after 4 months (95%CI)		p-value
		Usual follow-up	Nurse-led follow-up	Usual follow-up	Nurse-led follow-up	
EORTC QLQ-C30						
Functional scales (100=best)						
Physical	87	67 (7)	64 (7)	14 (10 to 21)	16 (12 to 21)	0.83
Role	85	46 (15)	45 (16)	23 (15 to 31)	24 (16 to 32)	0.84
Emotional	81	79 (10)	79 (10)	-3 (-9 to 3)#	5 (-1 to 11)	0.13
Cognitive	88	78 (9)	80 (9)	6 (0 to 11)	6 (0 to 11)	0.65
Social	87	69 (11)	74 (11)	11 (5 to 18)	8 (2 to 15)	0.58
Global health status	66	61 (6)	61 (7)	13 (8 to 18)	16 (11 to 21)	0.26
Symptom scales (0=best)						
Fatigue	19	52 (12)	53 (12)	-20 (-26 to -14)	-22 (-28 to -15)	0.92
Nausea/vomiting	2	22 (9)	21 (9)	-1 (-8 to 6)	-8 (-15 to -1)	0.08
Pain	20	18 (11)	24 (11)	-6 (-12 to 1)	-9 (-15 to -2)	0.61
Symptoms, single items (0=best)						
Dyspnoea	13	28 (11)	29 (12)	-11 (-18 to -4)	-10 (-17 to -3)	0.74
Insomnia	20	29 (17)	30 (17)	-9 (-17 to -1)	-7 (-15 to 1)	0.57
Appetite loss	6	38 (17)	41 (17)	-20 (-29 to -11)	-25 (-34 to -16)	0.77
Constipation	4	15 (8)	13 (9)	-7 (-13 to -1)	-5 (-11 to 1)	0.73
Diarrhoea	2	28 (14)	30 (15)	-4 (-12 to 4)	-11 (-19 to -3)	0.41
Financial difficulties	10	7 (9)	11 (9)	2 (-4 to 8)	0 (-6 to 6)	0.73
EORTC QLQ-OES18						
(0=best)						
Dysphagia scale		17 (7)	17 (7)	-5 (-11 to 1)	-6 (-12 to 0)	0.83
Eating scale		34 (10)	36 (10)	-6 (-13 to 0)	-11 (-17 to -5)	0.60
Deglutition scale		17 (8)	13 (8)	-3 (-11 to 4)	5 (-3 to 12)	0.40
Indigestion scale		-5 (11)	-2 (11)	5 (-2 to 13)	7 (-1 to 14)	0.44
Pain scale		12 (5)	10 (5)	-1 (-6 to 4)	-1 (-6 to 4)	0.53
Single items (0=best)						
Having dry mouth		28 (13)	33 (14)	-13 (-22 to -4)	-23 (-32 to -14)	0.32
Troublesome taste		21 (13)	26 (12)	-8 (-16 to 0)	-17 (-25 to -9)	0.46
Troublesome coughing		33 (13)	30 (13)	-10 (-18 to -1)	-15 (-23 to -6)	0.17
Troublesome talking		22 (12)	21 (12)	-10 (-17 to -2)	-12 (-21 to -4)	0.38
Euroqol						
(100=best)						
EQ-5D	76	70 (0)	66 (0)	9 (3 to 15)	10 (3 to 16)	0.56
Euroqol VAS scale		60 (5)	60 (5)	9 (5 to 13)	14 (10 to 19)	0.13
HAD scale						
(0=best)						
Total		10 (1)	10 (1)	-2 (-4 to 0)	-2 (-4 to 0)	0.79
Anxiety scale		5 (0)	5 (0)	0 (-1 to 1)	-1 (-2 to 0)	0.33
Depression scale		5 (0)	5 (0)	-2 (-3 to -1)	-1 (-2 to 0)	0.69

* For the EORTC QLQ-C30, scores of a general German population (n=390) of men between 60-69 years are given (33). For the EQ-5D, scores of a general Swedish population (n=1321) of men and women between 60-69 years are given (34). Norm scores were not available for the EORTC QLQ-OES18.
# A change of -3 means that HRQoL deteriorates with 3 points on a 100 point-scale 4 months after treatment.

Table 3. Satisfaction of patients and their partners at 7 months after randomisation for usual follow-up or nurse-led follow-up after oesophageal cancer surgery

	Type of follow-up	No. of patients	Mean (sd)	p-value	No. of spouse	Mean (sd)	p-value
Overall satisfaction rate (0-10)	Usual	45	7.9 (1.2)	0.14	35	7.4 (1.4)	0.03
	Nurse-led	46	8.3 (1.2)		33	8.1 (1.2)	

of nurse-led follow-up), both patient groups were satisfied with the time spent during follow-up visits. If patients were accompanied by their spouses during follow-up, an average of 15% of time was spent on the partners in the usual follow-up group compared to an average of 23% of time in the nurse-led follow-up group (p=0.004). Patients and spouses of the nurse-led follow-up group more often experienced the follow-up visits as expected (p=0.04 and p=0.03, respectively). If not satisfied with follow-up visits, patients and spouses had expected a systematic follow-up schedule with diagnostic tests and/or procedures for the detection of early recurrences. Compared to the usual follow-up group, patients and spouses of the nurse-led follow-up group received more often advice regarding disease management (p=0.04 and p=0.03, respectively). In addition, spouses of the nurse-led follow-up group more often had an opportunity to ask questions (p=0.06).

Functional outcome and survival

According to the protocol, patients were invited for five follow-up visits in the first year after surgery (both usual and nurse-led follow-up). This was established in 82% of patients in the nurse-led follow-up group and in 60% of the usual follow-up group. In the usual follow-up group, 25% of the patients (n=14) had more than 5 counselling episodes, compared to one (2%) patient in the nurse-led follow-up group (p=0.02). For 8 (15%) patients of the usual follow-up group an extra consult by telephone was planned between two scheduled follow-up visits, compared to 12 (22%) patients in the nurse-led follow-up group (p=0.30).

All patients experienced a change in eating pattern, resulting in the distribution of more meals over the day, which were divided into smaller portions. During follow-up, the majority of patients were able to eat a normal diet or were able to eat solid food with some difficulty (dysphagia score 0-1). Thirty-two (28%) patients developed dysphagia and these patients needed one or more (mean 3 ± 2, range 1-8) dilations for a benign anastomotic stricture (Table 4). The WHO performance score remained stable during follow-up (grade 0-1).

Eleven (20%) patients in the nurse-led follow-up group and 16 (29%) patients undergoing usual follow-up developed recurrent tumour and/or metastases at a median of 8 months after surgery (p=0.50). Of these, nine (33%) received palliative chemotherapy whereas five (19%) patients were treated with external beam radiation therapy. Fourteen (13%) patients died within the first year after surgery.

Table 4. Outcome and survival in 109 patients randomised to usual follow-up or nurse-led follow-up after oesophageal cancer surgery

	Usual follow-up n=55	Nurse-led follow-up n=54	p-value
Mean body weight; kg ± sd			
- 6-months visits	71 ± 14	74 ± 14	0.30
- 12-months visits	69 ± 15	75 ± 14	0.08
Post-operative dilation of anastomotic stricture; no. of patients (%)	15 (27)	17 (31)	0.63
Recurrent disease < 1 year after surgery; no. of patients (%)	16 (29)	11 (20)	0.31
- median time to recurrent disease; days	238	208	0.39
Died < 1 year after surgery; no. of patients (%)	7 (13)	7 (13)	0.97
- median survival; days	303	243	0.86

Costs

Costs of nurse-led follow-up visits were significantly lower than costs of usual follow-up visits (€232 vs. €453; p<0.001) (Table 5). Costs for intramural care were by far the highest cost category for both types of follow-up, but differences were not significant (nurse-led follow-up €1,477 vs. usual follow-up €2,277; p=0.19). Mean hospital stay was 8.9 days for nurse-led follow-up versus 17.8 days for usual follow-up (p=0.07). Costs for diagnostic procedures (nurse-led follow-up €588 vs. usual follow-up €689; p=0.34), additional treatments (€182 vs. €255; p=0.29) and extramural care (€111 vs. €74; p=0.97) were similar in both follow-up groups. Total costs were lower for nurse-led follow-up than for usual follow-up (€2,592 vs. €3,789), however, due to the large variation between patients, this difference was not statistically significant (p=0.11).

Uncertainty around the cost of a one point gain in the EQ-VAS is represented by a CEAC, which shows the probability that nurse-led follow-up is cost effective compared with the maximum that a decision maker is willing to pay for this outcome gain (Figure 3). The probability that nurse-led follow-up is cost effective reaches 91%, which is the level on which decision makers are no longer willing to pay for a one point gain on the EQ-VAS. The 13-month curve shows that a decision maker who is willing to pay €4000 or more for such a gain would find this care cost-effective with a probability of 20-25%. The 4-month EQ-VAS scores are relatively high for nurse-led follow-up (Table 2), resulting in a 98% probability that nurse-led follow-up is cost effective compared to outpatient clinic follow-up at a relatively low cost of €500 per patient.

Table 5: Average health care use and costs (in €) per patient during follow-up after oesophageal cancer surgery

Cost category	Usual follow-up n=55	Nurse-led follow-up n=54	p-value[5]
Costs follow-up visits	503	234	<0.001
Total intramural care[1]	2277	1477	0.19
Total diagnostic procedures[2]	689	588	0.34
Additional treatment[3]	255	182	0.29
Extramural care[4]	74	111	0.97
Total costs per patient	**3798**	**2592**	**0.11**

[1]Costs include hospital stay and visits to outpatient clinic
[2]Costs include diagnostic procedures for example endoscopy, X-ray, ct-scan
[3]Costs include additional treatment for example chemotherapy, radiation therapy
[4]Costs include for example visits to the general practitioner
[5]Derived from 2000 bootstrap samples drawn with replacement

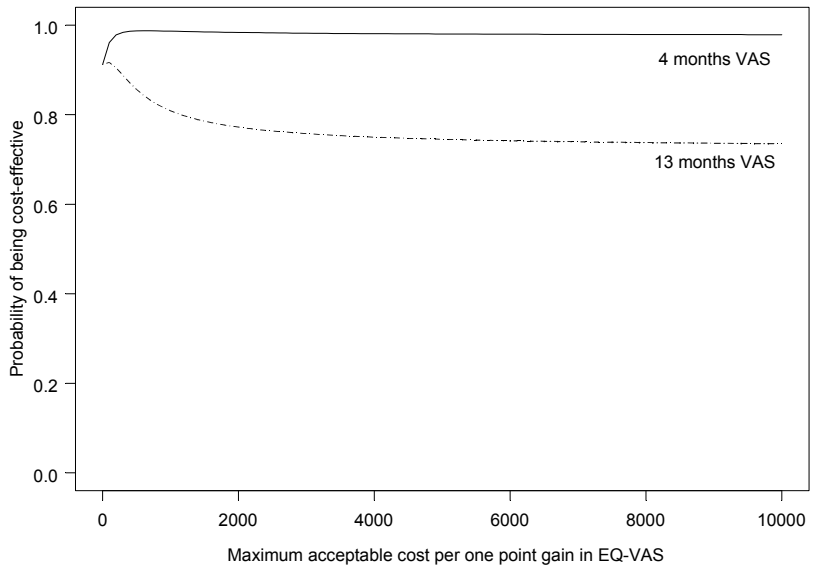

Figure 3. Cost effectiveness acceptability curve for nurse-led follow-up versus usual follow-up

DISCUSSION

This study shows that patients after curative oesophageal cancer surgery can safely be followed up at home by a specialist nurse. Nurse-led follow-up did not adversely affect quality of life and patients were satisfied with this type of care. Moreover, this alternative follow-up schedule is likely to be less costly than usual follow-up.

Over the last few years, nurses have increasingly become involved in the care of patients with malignancies (20). Results from the present study support this and suggest that nurses could also perform the follow-up of patients after oesophageal or gastric cardia cancer surgery. Involvement of nurses may not only be beneficial to patients for psychosocial support and advice, but also in identifying symptoms of disease, coordinating the type of care, and promoting health behaviour in this patient group in whom the detection of metastases usually means that only a palliative treatment option is available (35).

Faithfull et al. (36) evaluated the effectiveness of nurse-led follow-up versus usual medical care in patients undergoing pelvic radiotherapy. Nurse-led follow-up was focused on coping with symptoms and providing continuity of care. It was found that follow-up by a specialist nurse was effective in performing these tasks. A similar type of study was performed in patients with lung cancer (37). It was demonstrated that that nurse-led follow-up resulted in a more individualized care of patients, increased patient satisfaction, and a reduced number of hospital visits.

In the current study, the disease-specific EORTC QLQ-OES18 and the generic EORTC QLQ-C30 were used to evaluate HRQoL in these patients. The assessment of quality of life in patients with cancer may provide information about patients' perception of their health. In addition, it could play a role in decision-making on the relative effectiveness of various treatments and help in a patients' decision to undergo a certain treatment. Finally, information on quality of life could facilitate the communication between professional healthcare workers and patients (38, 39). We found no differences in disease-specific or generic quality of life scores over time between the two follow-up groups. At 13 months, scores on the role, cognitive and physical functioning scales still differed from those of a norm population in Germany, whereas scores on the emotional and social functioning scales were similar (33). Remarkably, scores of the global health status were somewhat higher for our patient group compared to the population norms. This suggests that the hope of surviving oesophageal cancer, which could be the consequence of undergoing an oesophageal resection, might give patients a considerable amount of optimism. Although the overall prognosis for oesophageal cancer is dismal with a 5-year survival rate of around 40% (40), it seems likely that patients are willing to accept some of the physical and other limitations after this type of surgery. In addition, it is conceivable that the longer the disease-free period exists, the higher the score on the overall health status will be. It has previously been reported that patients with a follow-up of 2 years or more after oesophageal resection and without evidence of tumour recurrence had general quality of

life outcomes comparable with reference values, although some symptoms, such as early satiety and appetite loss, fatigue, diarrhoea and/or psychological irritability, still persisted in that group (9, 11). In line with this, we found that in our study group various symptoms, such as nausea/vomiting, appetite loss, diarrhoea, fatigue and constipation, were still present 13 months after surgery. These results confirm that it takes a relatively long time for patients to recover from an oesophageal resection and to adjust to the new anatomical situation.

In our study, the 1-year survival rate was 87%. This is in contrast with results from other studies, in which survival rates varied between 65% to 71% (9, 13, 41). This may be explained by the selection of our patients. Patients who died in the peri-operative period or during the postoperative hospital stay, and patients who were admitted to a nursing home because of co-morbidity were excluded from our study. Another explanation could be that this was the result of an improvement in preoperative staging and patient selection for surgical resection, and an optimised peri- and postoperative protocol (4, 42).

Assessment of patient satisfaction can be used to monitor and improve quality of healthcare services and may provide information about the extent to which patients' needs and expectations are addressed (43, 44). In addition, satisfaction with care as an outcome measure allows monitoring the effect of a new intervention in healthcare. In our study, we evaluated follow-up of patients after oesophagectomy by regular home visits carried out by a specialist nurse as a new intervention. Although no differences were found in patient satisfaction between the nurse-led follow-up group and the usual follow-up group, spouses in the nurse-led follow-up group were more satisfied with this new type of care (Table 3). We speculate that this could be explained by the fixed and rather tight time schedule (10 minutes per patient) at the outpatient clinic, whereas the nurse was allowed to spend more time (a maximum of 30 minutes per patient) during follow-up visits to address the needs of patients as well as the needs of their spouses. Northouse et al. (45) assessed patients' and spouses' adjustment to colon cancer, starting at the time of diagnosis and continuing to one year post surgery. It was found that spouses reported significantly more emotional distress and experienced less social support than patients. They concluded that health professionals should include family caregivers in planned programs of care. In addition, professional support should be directed towards both patients and spouses, not only because both have legitimate needs for support, but also because role adjustment problems in spouses may negatively affect the long term adjustment of patients (45). Based on this trial, we recommend that problems and needs should be assessed throughout the follow-up period, not only in patients but also in their relatives.

An important part of this randomised study was a detailed cost analysis (Table 5). We found that usual follow-up was probably more expensive than nurse-led follow-up. It is remarkable that economic implications of nurses involvement in the oncological practice has been evaluated in only a few studies (36, 37, 46-49). All these studies concluded that nurse-led care was cost-effective. Our study differed from those of others in that in particular costs of follow-

up visits, and, although not significant, those of intramural care were lower in the nurse-led follow-up group. In addition, the cost effectiveness acceptability curve showed that, even when a decision maker is not willing to pay for an improvement in quality of life, nurse-led follow-up of patients after oesophageal or gastric cardia cancer surgery is almost always a cost-effective strategy.

In conclusion, this study shows that a specialist nurse can safely follow-up patients after oesophageal cancer surgery with curative intent. Nurse-led follow-up did not adversely affect quality of life and was likely to be more cost-effective than usual care. This type of follow-up may be an attractive alternative to routine follow-up by a surgeon in patients after oesophageal or gastric cardia cancer surgery, and probably also in patients with other types of cancer, particularly in those in which recurrent or metastastic cancer means that no curative treatment option is available. A well-designed nurse-led service may increase continuity of care and reduce the workload of physicians.

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4C

Outpatient clinic follow-up by a physician versus nurse-led follow-up at home after surgery for oesophageal cancer: a cost comparison study

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ABSTRACT

Costs of different follow-up strategies of patients after surgery for oesophageal cancer have so far not been evaluated. We therefore compared costs of usual outpatient clinic follow-up visits by a physician with those of nurse-led follow-up at home after surgery for oesophageal cancer. Hundred-nine patients were randomised to usual follow-up by a physician (n=55) or regular home visits by a specialist nurse (n=54). Cost comparisons included comprehensive data of hospital costs, diagnostic interventions and extramural care. Detailed information on health care consumption was obtained from a case record form at 6 weeks, and 3, 6, 9 and 12 months after randomisation. Patients after oesophageal cancer surgery can safely be followed by a specialist nurse, without affecting quality of life and with high patient satisfaction. In addition, total medical costs were lower for nurse led follow-up (€2,600 vs. €3,800) compared to those of usual follow-up, however, this was statistically not significant (p=0.11). This was mainly due to lower costs of nurse-led follow-up at home (€230 vs. €500; p<0.001), and a trend towards lower costs for total intramural care (1480 vs. 2280; p=0.20). In conclusion, nurse-led follow-up of patients after oesophageal cancer surgery is likely to generate cost savings. The results of this study add to the emerging evidence supporting the cost-effectiveness of nurses involved in counselling and treating patients with malignant diseases.

INTRODUCTION

The incidence of oesophageal cancer has risen dramatically over the past two decades in the Western world, due to a marked increase in the incidence of adenocarcinoma (1, 2). Despite recent advances in the curative treatment of oesophageal cancer (3), less than 50% of patients have operable disease at presentation. Surgery for oesophageal cancer is a serious life-event, which is often accompanied by significant morbidity and obviously, influencing quality of life of patients (4-9). It is well known that approximately 30% of patients will develop recurrent cancer within the first year after oesophageal resection. Treatment and counselling for physical and emotional problems are important issues during follow-up. Therefore, it is important that questions about treatment, disease-related symptoms and prognosis are adequately discussed. In addition, patients may need reassurance and emotional support during follow-up visits (10, 11).

Over the last few years, the role of nurses in clinical medicine has been expanding (12). As before, nurses are working to provide services which complement or extend those provided by physicians. Recently, however, nurses increasingly have been reported to perform tasks and procedures previously done d by physicians (13, 14). One of the ways in which nurses are involved in advanced clinical practice is by the introduction of nurse-led clinics in oncological care (15-18).

In the light of the commonly held view that nurse-led care may generate cost savings, it is remarkable that the economic implications of nurse working in the gastrointestinal and endoscopic practice has been evaluated in only a few studies (19-21). It has for instance been demonstrated that costs of flexible sigmoidoscopy (19, 20) or capsule endoscopy (21) are lower if performed by nurses compared to physicians. Costs were, however, only 'roughly' calculated, using charges and with little information about the differentiation of these costs. In the current healthcare environment, costs play an important role in clinical decision-making. Based on these considerations, nurse-led follow up could be a helpful way to decrease costs of follow-up after oesophageal cancer surgery. To date, there have been no cost-analysis studies comparing usual outpatient clinic follow-up visits by a physician with nurse-led follow-up after surgery for oesophageal cancer. Therefore, we performed a randomised trial, comparing total costs of these two follow-up regimens in patients that had undergone this type of surgery.

MATERIALS AND METHODS

Study population

We performed a prospective study in a university hospital (n= 105 patients) and a general hospital (n=4 patients). Between January 2004 and February 2006, 109 consecutive patients

who had undergone oesophageal resection were randomised to follow-up by physicians at the outpatient clinic (usual follow-up) or regular home visits performed by a specialist nurse (nurse-led follow-up). Inclusion criteria included surgery for carcinoma in the oesophagus or gastric cardia with curative intent, and written informed consent. The two follow-up groups were comparable with respect to patient characteristics (Table 1). Both follow-up groups consisted predominantly of males, with a mean age of 61 year. The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands.

Study endpoints

Clinical outcomes were health related quality of life (HRQoL), as measured by standardized questionnaires, at randomisation (at the outpatient clinic), and at 4, 7 and 13 months after randomisation (postal mailing), medical outcome, survival, patient satisfaction (7 months after randomisation) and costs. The clinical outcome has been presented in detail elsewhere (22). In the present study, we thoroughly evaluated medical costs of usual follow-up by surgeons and nurse-led follow-up by a specialist nurse. Costs were studied from a societal perspective and were estimated for a period of 12 months follow-up in a total of 95 (87%) patients or until death in 14 (13%) patients.

Data collection

Patients were randomised three weeks after hospital discharge, during the first visit to the outpatient clinic after the operation. The next follow-up visits were at six weeks, and three,

Table 1. Patient characteristics of 109 patients randomised to usual follow-up by a physician or nurse-led follow-up at home after oesophageal cancer surgery

	Usual follow-up n=55	**Nurse-led follow-up n=54**
Age; mean ± sd	61 ± 7	61 ± 9
Gender (male/female)	41/14	40/14
Median dysphagia score at baseline (IQR*)	0 (1)	0 (1)
Median WHO performance score at baseline (IQR)	1 (1)	1 (1)
Radiation and/or chemotherapy prior to surgery		
- Total	17 (31%)	14 (26%)
- chemotherapy	12	6
- radiation and chemotherapy	5	8
Surgical technique		
- transhiatal oesophagectomy	41 (75%)	43 (80%)
- transthoracic oesophagectomy	14 (25%)	11 (20%)
Mean postoperative hospital stay; days ± sd	23 ± 13	23 ± 16

* IQR = interquartile range

six, nine and twelve months after randomisation. The participating surgeons as well as the specialist nurse filled out standardized case record forms (CRFs) during the follow-up visits. For each patient, we registered the number of inpatient days, the use of diagnostic procedures and, if necessary, the palliative treatment modality that had been performed, and the visits to the outpatient clinic and general practitioners.

HRQoL was assessed using the oncology-specific European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 measure (23), the oesophageal cancer specific EORTC QLQ-OES18 measure (24), the EuroQol-5D measure (25), and the Hospital Anxiety and Depression scale (HAD) (26), whereas for satisfaction a questionnaire was developed for patients as well as their spouses.

Cost calculations

Real medical costs were calculated by multiplying the volumes of health care use with the corresponding unit prices. For the calculation of the total medical costs per patient, we distinguished intramural medical costs (inpatient days, health practitioner care, full cost prices of medical treatment and other medical procedures) and extramural medical costs (general practitioner). Costs caused by loss of production due to absence from work were not taken into account, because the majority of patients had already retired from work.

For the most important cost items, unit prices were determined by following the micro-costing method (27), which is based on a detailed inventory and measurement of all resources used. Costs for inpatient days in the hospital were estimated as real basic costs per day using detailed information from the financial department of the hospital. We made a distinction between costs of the university and the general hospital. These estimates included overhead and indirect costs. From a differential point of view, i.e., the comparison of the two treatment strategies, some diagnostic interventions were decided to be less relevant. We chose not to spend much time and effort in exploring costs that were unlikely to make any difference to the study result (28), for example in case these 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 the costs of medication use, average charges for analgesics, antibiotics and additional medications were used. We reported costs in Euro for the year 2006. Discounting was not relevant because of the limited time horizon.

Statistical analysis

All analyses were performed on an intention-to-treat basis. The cost differences between usual follow-up by physicians and nurse-led follow-up were analysed 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 (29).

RESULTS

Clinical outcome

The quality of life score of the two follow-up groups were not statistically significantly different (Table 2). Over time, a statistically significant and clinically relevant improvement in the eating scale (EORTC QLQ-OES18), and in the fatigue, physical, role and social functioning scales and global health (EORTC QLQ-C30) were found in both follow-up groups, whereas other scales, for example those for deglutition (EORTC QLQ-OES18) remained more or less stable.

In total, 11 (20%) patients in the nurse-led follow-up group and 16 (29%) patients undergoing usual follow-up developed metastases at a median of 8 months after surgery (p=0.31). Of these patients, nine (33%) received palliative chemotherapy and five (19%) patients were treated with external beam radiation therapy. Fourteen (13%) patients died within the first year after surgery. These findings were equally distributed between the two follow-up groups.

Costs

A cost-minimization analysis was performed, since the clinical and quality of life outcomes of both patient groups were not different and therefore only costs had to be compared (27, 28).

Table 2. Outcome in quality of life of 109 patients randomised to usual follow-up or nurse-led follow-up after oesophageal cancer surgery at 13 months of follow-up

	Usual follow-up n=55		**Nurse-led follow-up n=54**
EORTC QLQ-C30[1]			
- functional scales		no differences	
- symptoms scales		no differences	
- global health status (0-100)*	71		73
EORTC QLQ-OES18[2]			
- scales related to food intake		no differences	
- single item scales		no differences	
- pain scale (100-0)*	10		9
EuroQol-5D (0-100)*	74		76
HAD scale			
- anxiety scale (0-21)*	5		5
- depression scale (0-21)*	4		3

* p=NS

[1] The EORTC QLQ-C30 incorporates five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, nausea/vomiting, pain), and a global health/quality of life scale.

[2] The EORTC QLQ-OES18 incorporates five multi-item scales (dysphagia, eating, deglutition, indigestion, pain) and four single symptoms scales (having a dry mouth, troublesome taste, troublesome coughing, troublesome talking).

Table 3 gives an overview of the average health care use and costs per patient for usual and nurse-led follow-up of patients after oesophageal cancer surgery. The total average costs per patient were higher for usual follow-up compared to nurse-led follow-up (€3,800 vs. €2,600; p=0.11), although this difference did not reach statistically significance. Initial costs for nurse-led follow-up visits were lower than costs of usual follow-up (€234 vs. €503; p<0.001). According to the protocol, patients were invited for five follow-up visits in the first year after surgery (both usual and nurse-led follow-up). This was established in 82% of patients in the nurse-led follow-up group and in 60% of the usual follow-up group. In the usual follow-up group, 25% of the patients (n=14) had more than 5 counselling episodes, compared to one (2%) patient in the nurse-led follow-up group (p=0.016).

The costs for intramural care were the highest cost category for both types of follow-up, and were higher for usual follow-up than for nurse-led follow-up (€2,277 vs. €1,477), but these differences were again statistically not significant (p= 0.20). The mean length of hospital stay for admitted patients was also higher for patients randomised to usual follow-up compared to nurse-led follow-up (17.8 versus 8.9 days; p= 0.07). In both groups, 43 patients (>75%) had not been admitted to a hospital or nursing home. Patients randomised to nurse-led follow-up were on average admitted for a longer period in a nursing home (2.5 versus 0.4 days). This was, however, largely due to the admission of one patient, who stayed in a nursing home for a total period of 127 days.

Costs of diagnostic procedures during follow up were slightly, but not statistically significantly higher in the usual follow-up group compared to the nurse-led follow-up group (€690 vs. €590; p=0.34). The average costs for a general practitioner were €111 for nurse-led follow-up and €74 for usual follow-up (p=0.97).

DISCUSSION

In the present study, we compared home visits by a specialist nurse with usual follow-up visits by a physician to the outpatient clinic with regard to costs in a group of patients after surgery for oesophageal cancer. Nurse-led follow-up was found to be less costly compared to usual follow-up. This was mainly due to lower costs of the follow-up visits and those of intramural care. In another study, we recently reported that patients after oesophageal cancer surgery could safely be followed up by a specialist nurse without adversely affecting quality of life of patients and with a high patient satisfaction (22).

As far as we are aware of, no previous studies have compared costs of nurse-led follow up with those of usual follow-up visits to the outpatient clinic in patients after oesophageal cancer surgery. Some studies have, however, analysed the economic implications of nurses working in the endoscopic practice (19-21). These studies all found that costs were lower if examinations, particularly sigmoidoscopy and video capsule endoscopy, were performed

Table 3. Average health care use and costs (€, 2006) per patient during usual follow-up by a physician or nurse-led follow-up at home after oesophageal cancer surgery

Cost category		Usual follow-up n=55		Nurse-led follow-up n=54		95% CI[a] Mann-Whitney
	Cost prize	Volume	Costs	Volume	Costs	
Costs follow-up visits		5.0	**503**	4.7	**234**	<0.001 (230 to 303)
Total intramural care						
Inpatient days						
- Hospital (academic)	553	1.9	1046	0.4	202	
- Hospital (general)	405	2	802	1.4	585	
- Nursing home/hospice	184	0.4	70	2.5	453	
Outpatient clinic						
- Physician (academic)	144	2.1	304	1.35	195	
- Physician (general)	104	0.5	55	0.4	42	
			2277		**1477**	0.19 (-1252 to 2412)
Total diagnostic procedures						
X-ray thorax/abdomen/skeleton	60	0.4	24	0.4	23	
Ultrasound neck/abdomen	45	0.1	5	0.0	0	
CT-scan	140	0.8	107	0.3	39	
MRI	234	0.1	21	0.1	26	
Blood tests	Variable		59		12	
Histology biopsies	50	0.1	3	0.1	3	
Laryngoscopy	87	0.1	8	0.0	3	
Gastroscopy (+dilation)	345 (+42)	1.2	457	1.3	479	
Colonoscopy	75	0.1	5	0.0	3	
			689		**588**	0.34 (-242 to 323)
Total additional treatment						
Chemotherapy	368	0.7	248	0.3	95	
Radiation	19	0.4	7	0.2	4	
Stent placement	1600	0.0	0	0.1	83	
			255		**182**	0.29 (-234 to 314)
Extramural care						
General practitioner (inpatient)	20	1.8	35	2.7	54	
General practitioner (home visits)	39	1.0	39	1.5	57	
			74		**111**	0.97 (-64 to 7)
Total costs per patient			**3798**		**2592**	0.11 (-824 to 2972)

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

by a specialized trained nurse instead of a physician. In another study, nurse-led follow-up care for patients undergoing pelvic radiotherapy was compared with conventional medical care (15). Results from that study suggested that a specialist nurse was able to provide a safe follow-up of patients undergoing radiotherapy. Furthermore, nurse-led follow-up resulted in a 31% reduction in costs.

Our study suggests that nurse-led follow-up is able to correct the pattern of use of medical services. It was found that fewer diagnostic procedures and less palliative treatments were performed in patients in the nurse-led follow-up group compared to those followed-up by a physician. It is speculated that nurse-led follow up may reduce the number of routine diagnostic investigations in patients after oesophageal cancer surgery without compromising patient safety. In this regard, it is important to realize that the early detection of recurrent tumour after oesophageal cancer surgery currently prompts a physician to palliate coexisting symptoms, as, for now, a curative treatment option is not available. On the other hand, patients in the nurse-led follow-up group more often visited or were visited by a general practitioner. These differences can be interpreted as evidence that some substitution of medical input to nursing occurred in the nurse led follow-up group, which probably resulted in the use of a more appropriate mixture and location of care. Counselling and treatment of physical and emotional problems are important items during follow up visits of a patient after oesophageal cancer surgery. Nurse-led follow up can be used to reconfigure care to make it more responsive to individual needs, and reduce the burden of hospital visits and investigations to patients.

Follow-up of patients with a high risk of developing metastases is demanding, since the mortality rate is high (30). In a palliative setting, it is sometimes difficult to differentiate between health care consumption that can be attributed to the palliative stage of the disease or only to the treatment modality. For instance, the prolonged period of time that some of the patients were admitted in a hospital and/or nursing home (with extremes of 145, 72, and 44 days in the present study) may not directly be related to the follow-up itself, but more to the advanced stage of the disease. However, even when we omitted these 'palliation-related costs' out of consideration, did not affect the final conclusion that nurse-led follow-up of this patient group was (non-significantly) cheaper. It is important to realize that the relative lower costs of nurses, compared to those of physicians, is counterbalanced by the level of the medical staff that is replaced and the extent of supervision that is required by nurses. In other words, the cost saving in lower salaries of nurses might be offset by the need for a supervising consultant of nurses (31).

It has been suggested that nurses could also be involved in the management of patients with chronic gastrointestinal disorders, such as, inflammatory bowel disease, Barrett's oesophagus, chronic pancreatitis and irritable bowel syndrome (32, 33). In addition, nurses could well play a role in the palliative care of patients with incurable or recurrent cancer of the gastrointestinal tract, for example oesophageal cancer, gastric cancer and pancreatic

cancer (34, 35). We are currently performing a randomised trial to evaluate the effect of nurses' involvement during follow-up of patients in a palliative stage of oesophageal, pancreatic and hepatocellular cancer. Quality of life, medical effects, satisfaction and costs are also the main outcome measures of that study.

The need for efficient patient education and counselling is growing with the ongoing development of new medical technologies. Studies have shown that patient education conducted by nurses may be beneficial to ensure compliance (36-38). In a study investigating a pre-endoscopy patient education program, it was found that patient education before an endoscopic procedure was able to reduce the rate of examination failures and their attending costs (36). In addition, optimal information to patients may benefit patient satisfaction and decrease anxiety.

In conclusion, the results of this study add to the emerging body of evidence supporting the cost-effectiveness of nurse involved in counselling, treating and following patients with different types of diseases, and should be taken into account by decision-makers planning health services. Clinical guidelines and supervision of physicians are recommended to support nurses in daily practice. In addition, it is important that patients with specific types of disorders are discussed in regular multidisciplinary meetings attended by all medical staff involved in the care of these patients.

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5

Palliative treatment of esophageal carcinoma

5A

A new design esophageal stent (Niti-S stent) for the prevention of migration: A prospective study in 42 patients

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ABSTRACT

Background: Covered rather than uncovered metal stents are used for the palliation of dysphagia from esophageal cancer, but a major drawback is the risk of stent migration, which occurs in up to 20% of patients. To overcome this problem, a double-layered stent, the Niti-S stent (Teawong Medical, Seoul, Korea), has been developed. The Niti-S stent consists of an inner polyurethane layer to prevent tumor ingrowth and an outer uncovered nitinol wire tube to allow the mesh of the stent to embed itself in the esophageal wall.

Methods: Between June 2003 and May 2004, 42 patients with malignant dysphagia caused by inoperable carcinoma of the esophagus or gastric cardia were treated with a Niti-S stent. Patients were prospectively followed and data collection focused on recurrent dysphagia, functional outcome, complications, and survival.

Results: At 4 weeks, the dysphagia score had significantly improved from a median of 3 (liquids only) to 0 (ability to eat a normal diet). Five of 42 (12%) patients with a Niti-S stent developed recurrent dysphagia, mainly due to tissue overgrowth (2 of 42; 5%) and stent migration (3 of 42; 7%). Major complications (perforation [1], aspiration pneumonia [2] and hemorrhage [2]) occurred in 5 of 42 (12%) patients. Pain following stent placement was observed in 5 of 42 (12%) patients and symptomatic gastro-esophageal reflux occurred in 2 of 42 (5%) patients.

Conclusions: The Niti-S stent provides symptomatic relief of malignant dysphagia and effectively reduces recurrent dysphagia. Its double-layered design is probably important in preventing the migration. In addition, the complete covering of the Niti-S stent may be a factor in preventing tissue overgrowth at both ends of the stent.

INTRODUCTION

The management of carcinoma of the esophagus and gastric cardia remains a major medical challenge. Despite recent advances in the curative treatment of esophageal cancer (1), 50-60% of patients have incurable disease at presentation. For them, only palliative therapy is possible. The goal of such therapy is to relieve dysphagia, the cause of much distress to these patients. Metal stents have become popular in the palliation of patients with malignant esophageal obstruction (2). Both uncovered (3, 4) and covered (5) metal stents have been shown to be associated with fewer (procedure-related) complications, such as bleeding and perforation, than the previously used non-expanding stents.

There are three main types of metal stents available: 1) the Ultraflex stent (Boston Scientific, Natick, USA) (3, 6-11), 2) the Wallstent (Boston Scientific, Natick, USA) (4, 12-16) with a modification on this design, the Flamingo Wallstent (10, 11, 17), and 3) the Z-stent (Wilson-Cook Europe, Bjaeverskov, Denmark) (5, 10, 18-22) with a Korean version (Shoo stent; Sooho Meditech, Seoul, Korea) (23, 24). These stents all offer the same degree of palliation of dysphagia caused by to inoperable esophagogastric carcinoma. Moreover, there are no statistically significant differences in the occurrence of complications and recurrent dysphagia between each of these three types of metal stents (10, 11).

Covered stent are now the most commonly used metal stents in patients with esophageal cancer. The cover avoids ingrowth of tumor through the metal mesh, which occurs in more than 25% of patients with an uncovered stent in the esophagus (25). However, covered metal stents are more likely to migrate than bare metal stents (2). In a recent study of 108 patients with dysphagia from inoperable cancer of the esophagus or gastric cardia, in whom a covered Ultraflex stent was placed, stent migration was observed in 18 (17%) patients, necessitating a reintervention in almost all of them (26).

To overcome the problem of stent migration, the Niti-S stent (Taewong Medical, Seoul, Korea) was developed for the palliation of malignant dysphagia (Figure 1A-B). This new device combines two specific characteristics, which presumably could reduce, if not eliminate, stent migration. First, the Niti-S stent flares at both ends. Second, it has a double-layer configuration with an outer uncovered nitinol wire tube to allow the stent to fix itself in the esophageal wall.

The aim of this study was to evaluate the Niti-S stent in patients with inoperable carcinoma of the esophagus or gastric cardia. Prospective data collection focused on recurrent dysphagia, functional outcome, complications and survival.

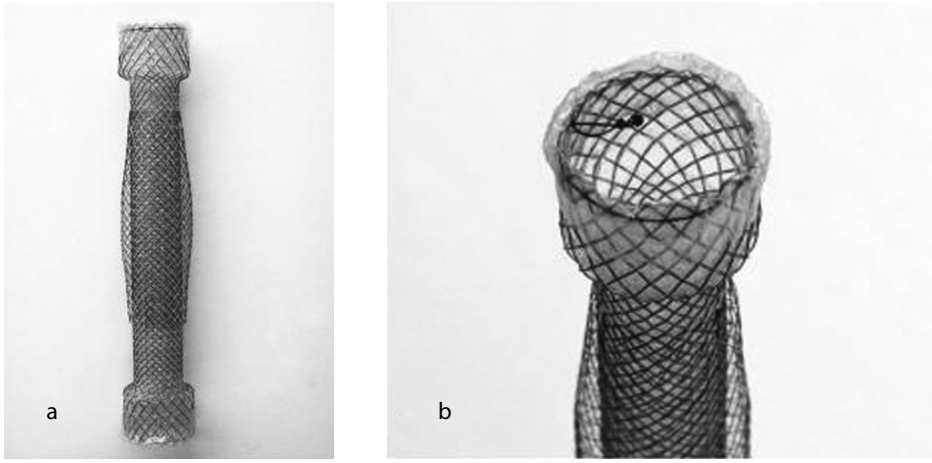

Figure 1. Niti-S stent with a double-layer configuration, consisting of an inner polyurethane layer and an outer uncovered nitinol wire (A). The stent flares to 26 mm at both ends (B).

PATIENTS AND METHODS

Study design

Patients with dysphagia caused by inoperable carcinoma of the esophagus or gastric cardia were eligible for this study. Inclusion criteria included inoperable malignant obstruction of the esophagus or gastric cardia (a tumor was considered inoperable if the patient had distant metastases, local tumor infiltration in neighboring organs, or a poor health due to concomitant disease), recurrent dysphagia after prior radiation with curative or palliative intent for esophageal cancer, and signed informed consent. Exclusion criteria were a lesion longer than 12 cm, tumor growth within 2 cm of the upper esophageal sphincter, a fistula between the esophagus and respiratory tree, previous metal stent placement, a World Health Organization (WHO) performance score of 4, or a patient unfit to undergo conscious sedation.

Patients were evaluated before stent placement, at 14 days and 4 weeks after placement, and then monthly until death. For patients still alive at the end of the study (November 30, 2004), follow-up was at least 6 months. Evaluations were performed by telephone, and included the following items: 1) ability to eat and/or swallow (graded as follows: 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 grade 4: complete dysphagia) (5); 2) general health as assessed by the WHO performance score (graded as follows: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time; and 4 = 100% bedridden); and 3) specific symptoms such as pain, heartburn, regurgitation, and weight loss. All evaluation items were recorded in a case record form.

Table 1. Clinical characteristics of 42 patients treated with a Niti-S stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

Characteristic	Value
Mean age in years (± SD)	65 ± 14
Gender; no. of patients (%)	
Male	25 (60)
Female	17 (40)
Median dysphagia score before treatment (IQR)	3 (2)
Median WHO performance score before treatment (IQR)	0 (3)
Mean tumor length in cm (± SD)	7.8 ± 2.4
Tumor location; no. of patients (%)	
Esophagus	33 (79)
Cardia	9 (21)
Tumor histology; no. of patients (%)	
Squamous cell carcinoma	10 (24)
Adenocarcinoma	32 (76)
Prior radiation and/or chemotherapy; no. of patients (%)	
Chemotherapy	6 (14)
Radiation	1 (2)
Both	2 (5)
Total	9 (21)

IQR: Interquartile range

Patients

Between June 2003 and May 2004, 42 patients with malignant dysphagia were enrolled in the study. They had been diagnosed with inoperable squamous cell carcinoma (n=10), and adenocarcinoma (n=32) of the esophagus and gastric cardia (Table 1). Niti-S stent placement was performed in two hospitals in The Netherlands, the Erasmus MC University Medical Center Rotterdam (n=39), and Rijnstate Hospital Arnhem (n=3). Written informed consent was obtained from all patients before enrollment. The study was approved by the Institutional Review Board of both hospitals.

Niti-S stent

The Niti-S stent is delivered in a compressed form inside an introducer sheath with a diameter of 20 Fr. The stent has a double-layer configuration, consisting of an inner polyurethane layer and an outer uncovered nitinol wire (Figure 1A). It is available in 3 lengths: 90 mm, 120 mm and 150 mm. The stent flares to 26 mm at its proximal and distal ends with a body diameter of 18 mm (Figure 1B). A thread is attached inside the proximal flange of the stent. When being pulled, the thread reduces the diameter of the stent "throat", enabling repositioning or removal of the stent. During stent insertion, all patients were consciously sedated with

midazolam (Dormicum®, Roche Nederland BV, Mijdrecht, the Netherlands). If necessary, the stricture was dilated to 9 mm to facilitate endoscope passage and to allow the tumor to be inspected, the tumor margins to be marked and a guidewire to be placed. The upper and lower tumor margins were marked with sclerotherapy needle-injected radiographic contrast material. The stent was advanced over a guidewire into the esophagus. After insertion, the stent was deployed under fluoroscopic monitoring, which is necessary because the Niti-S stent shortens approximately 35% after placement. A stent of 2-4 cm longer than the stricture was chosen to allow for a 1-2 cm extension above and below the proximal and distal tumor shoulder.

Statistical analysis

The following variables were included in assessing the outcome: 1) clinical characteristics (age, gender, dysphagia score before stent placement, WHO performance score before stent placement, indication for stent placement, tumor length, tumor location, histology, dilation before stent placement, and prior radiation and/or chemotherapy), 2) outcome and survival (dysphagia score after stent placement, 30-day mortality, survival and cause of death), and 3) complications and recurrent dysphagia.

The results were expressed as means ± standard deviation (SD), and medians and interquartile range; survival was expressed as median survival. Differences in dysphagia score before treatment and 4 weeks after treatment and WHO performance score before and 4 weeks after treatment were analyzed by the Wilcoxon rank-sum test. All analysis was performed on an intention-to-treat basis. A p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 10.1 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

Clinical characteristics of the patients treated with the Nit-S stent are shown in Table 1. In approximately one-quarter of patients, the tumor was located in the gastric cardia, whereas the remainder of tumors was in the esophagus.

Outcome and survival

Placement of a Niti-S stent was successful in all but one patient (Figure 2A to 2C). In one patient, the stent was retrieved endoscopically because it had deployed proximal to the tumor. A second Niti-S stent was successfully inserted during the same procedure. In 7 of 42 (16%) patients, dilation to 9 mm was performed prior to stent placement (Table 2). Dysphagia score significantly improved for all patients with a median of 3 (liquids only) before stent place-

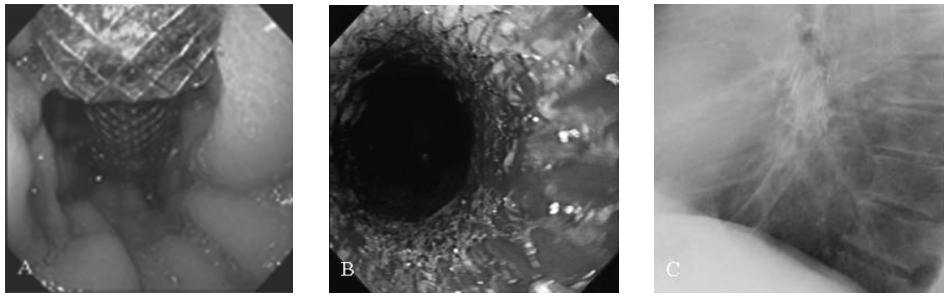

Figure 2. Endoscopic views of an expanding Niti-S stent just after insertion seen from the stomach (A). Endoscopic view inside the stent (B). On X-ray film, the stent is positioned partially in the esophagus and expanding below the diaphragm (C).

ment to a median of 0 (ability to eat a normal diet) 4 weeks after stent placement ($p<0.0001$). The WHO performance status deteriorated only slowly (Table 2).

Median survival after placement of a Niti-S stent was 139 days (Table 2). The majority of patients with a Niti-S stent (71%) died as a result of tumor progression within the 6-month follow-up period. Two (5%) patients died of septic complications following aspiration pneumonia after stent placement (see below).

Recurrent dysphagia and complications

Five of 42 (12%) patients with a Niti-S stent developed recurrent dysphagia, which was caused by tissue overgrowth (2 of 42; 5%) or stent migration (3 of 42; 7%) (Table 3). In one patient, tissue overgrowth occurred 118 days after stent placement at the proximal end of the stent. Biopsies were not taken. The stent was repositioned endoscopically to a level above the tis-

Table 2. Outcome and survival of 42 patients treated with a Niti-S stent

Characteristic	Value
Dilation before treatment; no. of patients (%)	7 (17)
Median dysphagia score 4 weeks after treatment (IQR)	0 (3)
Median WHO performance score 4 weeks after treatment (IQR)	1 (4)
30-day mortality; no. of patients (%)	3 (7)
Median survival in days	139
All deaths	32 (76)
Cause of death; no. of patients (%)	
Stent-related	2 (5)
Tumor progression	30 (71)

IQR: Interquartile range

Table 3. Complications and recurrent dysphagia in 42 patients treated with a Niti-S stent

Complication	Number of patients (%)
Total complications	13 in 11 pts (26)
Major complications	5 in 5 pts (12)
≤ 7 days	
Perforation	1
(Aspiration) pneumonia	2
> 7 days	
Hemorrhage	2
Minor complications	7 in 7 pts (17)
Mild retrosternal pain	5
Gastro-esophageal reflux	2
Recurrent dysphagia	5 in 5 pts (12)
Tumor regrowth	2
Stent migration	3*

*Tumor location in these patients included mid esophagus (n=1) and distal esophagus (n=2)

sue overgrowth. The second patient received palliative chemotherapy after stent placement. Despite a good initial response, overgrowth at the proximal end of the stent occurred 88 days after the last course of chemotherapy. A second overlapping stent was successfully inserted.

Stent migration occurred 6, 153 and 159 days after Niti-S stent placement. Tumor location in these patients included the mid-esophagus (n=1) and distal esophagus (n=2). In one patient, endoscopy showed that the stent had migrated into the stomach, so it was repositioned through the stricture in the esophagus. In another patient presenting with recurrent dysphagia, the stent could not be detected by endoscopy or plain abdominal radiography; it probably had passed the digestive tract without causing symptoms. Since the patient was in a terminal stage of the disease, no new stent was placed and the patient died 4 weeks later of tumor progression. In the third patient, the stent had only partially migrated and was repositioned endoscopically.

In total, major and minor complications were seen in 11 of 42 (26%) patients treated with a Niti-S stent. Major complications occurred in 5 of 42 (12%) patients (Table 3). In three patients, the major complications were related to the procedure. Two patients developed aspiration pneumonia within 24 hours after stent placement; both patients died of septic complications. In the third patient, a small perforation occurred as a consequence of dilation prior to stent placement; this was treated by the placement of a Niti-S stent, which completely covered the perforation. At the end of the study (6 months' follow-up), the patient was still alive. Two patients developed hemorrhage 138 and 229 days after stent placement (Table 3). In one patient with a stent across the gastro-esophageal junction, endoscopy showed reflux-esophagitis grade D, which was treated with proton-pump inhibitors. The second patient

presented with hematemesis, and endoscopy revealed the tumor as the most likely cause of the hemorrhage while the patient was receiving high-dose warfarin. The patient received a blood transfusion and the warfarin dose was reduced.

Minor complications, mainly symptoms of retrosternal pain and gastro-esophageal reflux, were seen in 7 of 42 (17%) patients (Table 3). The pain seemed to be stent-related in all patients. Most of these patients required analgesics at least temporary, and one patient was treated with narcotics.

Complications were not different between patients who had undergone prior radiation and/or chemotherapy (RCT) (Table 1) and those who had not (major complications: prior RCT: 1 of 9 (11%) vs. no prior RCT: 4 of 33 (12%), p=NS; minor complications: prior RCT: 3 of 9 (33%) vs. no prior RCT: 4 of 33 (12%), p=NS).

DISCUSSION

In this prospective follow-up series of 42 patients treated with a Niti-S stent for dysphagia due to inoperable carcinoma of the esophagus or gastric cardia, we showed that this new design stent provided good symptomatic relief of malignant dysphagia. Placement of the Niti-S stent was safe and not associated with more complications than other stents currently available (2). Recurrent dysphagia due to stent migration and tissue overgrowth was low in patients treated with a Niti-S stent (Table 3).

One of the remaining challenges in the palliative treatment of dysphagia with stents is the prevention of recurrent dysphagia. Stent migration has been described to occur in up to 28% of patients treated with a covered stent (10, 18, 25-29). Migration is more likely to occur with stents placed across the gastro-esophageal junction than with stents placed for tumors more proximal in the esophagus, probably because in this position the distal part of the stent projects freely into the fundus of the stomach and is thus unable to fix itself to the wall of the esophagus (2).

It has been recognized that the design of the stent may play a role in reducing stent migration. For example, the Flamingo Wallstent, was designed with a shift in the braiding angle between the proximal and the distal part of the stent, which allows the distal part of the stent to stretch in response to peristalsis (2). The Ultraflex stent and the (Flamingo) Wallstent are both available with uncovered proximal and distal segments, which allow the normal mucosa above and below the tumor to project into the stent lumen. The European version of the Z-stent has metal barbs on the outside of the stent to anchor it into the tumor (2).

The Niti-S stent was designed to reduce, if not eliminate, stent migration (Figure 1A and 1B). This new device combines two specific characteristics. First, the Niti-S stent flares to 26 mm at both ends (Figure 1B); this size was chosen to minimize the risk of stent-related complications to the esophagus (17). Second, it has a double-layer configuration, consisting of an inner

polyurethane layer to prevent tumor ingrowth and an outer uncovered nitinol wire tube to allow the mesh of the stent to embed itself in the esophageal wall (Figure 2A to 2C).

In our opinion, the greatest contribution to the prevention of stent migration comes from the friction exerted by the wire on the outside of the Niti-S stent to the esophageal wall. We were able to demonstrate that the Niti-S stent was resistant to migration in 39/42 (93%) patients (Table 3). In one of the three patients in whom the stent migrated, this occurred within the first few days after stent placement, suggesting that the stent had not yet fully expanded and settled.

Apart from migration, recurrent dysphagia due to tissue growth at both ends of the stent was also uncommon after Niti-S stent placement (2 of 42; 5%). Tissue overgrowth may be caused by non-malignant tissue growth at the end of a stent or by tumor overgrowth. Mayoral et al. (30) reported that recurrent dysphagia was caused by nonmalignant obstructive tissue, such as granulation tissue, reactive hyperplasia and fibrosis at the proximal or distal end of the stent, in 32% of patients after a mean interval of 22 weeks. Cwikiel et al. (31) placed uncovered stents in the esophagus of five patients. Significant strictures caused by fibrosis and proliferation of granulation tissue occurred in three of the five patients after 4, 5 and 7½ months, respectively. The last patient underwent an esophageal resection; histopathology examination showed mucosal denudation, deep impaction of the stent mesh into the esophageal wall, and the development of new reactive strictures at both ends of the stent.

Because most patients with a stent for inoperable esophageal or gastric cardia cancer have only a limited survival (in the present study a median survival of just over 4 months), reactive tissue growth at stent ends is an unlikely cause of recurrent dysphagia in these patients. This could be a problem if stents are left in the esophagus for a longer time, for example in benign strictures. The most common cause of recurrent dysphagia in this group of patients is probably still overgrowth by tumor tissue. Prevention of tumor overgrowth should be an important issue in future stent design.

In total, complications occurred in 11 of 42 (26%) patients (Table 3). Remarkably, two patients died from septic complications due to aspiration pneumonia following Niti-S stent placement. One patient experienced hematemesis, which was caused by the presence of severe esophagitis due to gastroesophageal reflux. In our institution, we usually prescribe proton pump inhibitors to inhibit gastric acid secretion, advise patients to sleep in an upright position, recommend avoiding late-night meals. Recently, stents with a "windsock"-type anti-reflux valve have become available (32). These stent types have been developed for the prevention of gastroesophageal reflux, particularly when the stent extends below the lower esophageal sphincter (2).

In conclusion, our results demonstrate that the Niti-S stent is a safe and effective device for the palliation of dysphagia in patients caused by inoperable cancer of the esophagus or gastric cardia. The incidence of procedure-related complications is comparable to that of other covered metal stents. The outer wire of the Niti-S stent is likely to reduce stent migra-

tion in patients with esophagogastric malignancies. In addition, the design of this stent may be a factor in preventing the occurrence of tissue overgrowth at the ends of the stent. We recognize that this is only a small study with a limited number of patients. Therefore, future randomized trials between covered stents of various designs are needed to compare efficacy, risk of complications and recurrent dysphagia, with particular attention given to stent migration and tumoral and nontumoral tissue overgrowth.

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5B

New esophageal stents for the palliation of dysphagia from esophageal or gastric cardia cancer: a randomized trial

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ABSTRACT

Background & aim: Stents are often used for the palliation of inoperable esophageal or gastric cardia cancer. One of the drawbacks of the currently used stents is the high percentage of recurrent dysphagia due to stent migration and tissue growth. New stents have been designed to overcome this unwanted sequel of stent placement. In the present study, we investigated whether results of stent placement could be improved with newer stent designs.
Methods: Between June 2004 and May 2006, 125 patients with dysphagia from inoperable carcinoma of the esophagus or gastric cardia were randomized to placement of an Ultraflex stent (n=42), Polyflex stent (n=41) or Niti-S stent (n=42). Patients were followed by scheduled telephone calls at 14 days after treatment, and then monthly for six months or until death. Technical and functional outcome, complications, recurrent dysphagia and survival were analyzed with, chi-square tests, Kaplan-Meier curves and log rank tests.
Results: Stent placement was technically successful in all patients with an Ultraflex stent, in 34/41 (83%) patients with a Polyflex stent and in 40/42 (95%) patients treated with a Niti-S stent (p=0.008). Dysphagia score improved from a median of 3 (liquids only) to 1 (ability to eat some solid food) in all patients. There were no differences in complications between the three stent types. Recurrent dysphagia, caused by tissue in- or overgrowth, migration or food obstruction, was significantly different between patients with an Ultraflex stent and patients with a Polyflex stent or Niti-S stent (22 (52%) vs. 15 (37%) vs. 13 (31%); p=0.03). Stent migration occurred more frequently with Polyflex stents, and tissue in- or overgrowth more frequently with Ultraflex stents. No differences were found in survival (median survival: Ultraflex stent 132 days vs. Polyflex stent 102 days vs. Niti-S stent 159 days) between the three stent types.
Conclusions: All three stents are safe and offer adequate palliation of dysphagia from esophageal or gastric cardia cancer. Nonetheless, Polyflex stents seem the least preferable in this patient group as placement of this device is technically demanding and associated with a high rate of stent migrations.

INTRODUCTION

Despite recent advances in the curative treatment of esophageal and gastric cardia cancer (1), more than 50% of patients have inoperable disease at presentation. For these patients, palliative treatment to relieve progressive dysphagia is usually the only treatment option. Self-expanding metal stents are often used for the palliation of obstruction from inoperable esophageal or gastric cardia cancer (2). One of the drawbacks of the presently used stents is the high percentage of recurrent dysphagia due to stent migration and tissue growth. New stents have been designed to overcome this unwanted sequel of stent placement.

Two newly designed stents, the fully-covered Polyflex stent (Rüsch AG, Kernen, Germany) and the Niti-S stent (Taewoong Medical, Seoul, Korea), were recently introduced with the specific objective to overcome the problem of recurrent dysphagia. The completely covered Polyflex stent is a silicone device with an encapsulated monofilament braid made of polyester (3). This material has been proposed to be able to reduce nontumoral tissue in- and overgrowth (4). The Niti-S stent combines two specific characteristics to reduce stent migration. First, the Niti-S stent flares to 26 mm at both ends. Second, it has a double layer configuration, consisting of an inner polyurethane layer over its entire length and an outer uncovered nitinol wire tube to allow the mesh of the stent to embed itself in the esophageal wall (5).

The aim of this study was to compare the worldwide most commonly used Ultraflex stent, with the newly-designed Polyflex stent and Niti-S stent in patients with dysphagia from carcinoma of the esophagus or gastric cardia.

METHODS

Study population

Between June 2004 and May 2006, 125 patients with dysphagia due to esophageal or gastric cardia cancer were randomized to treatment with an Ultraflex stent, Polyflex stent or Niti-S stent (Figure 1). Inclusion criteria included an inoperable malignant obstruction of the esophagus or gastric cardia, or recurrent dysphagia after prior radiation with curative or palliative intent for esophageal cancer. A tumor was considered inoperable if the patient had distant metastases or local tumor infiltration in neighboring organs (as defined by the TNM-classification), and/or a poor health because of concomitant disease. All patients gave written informed consent. Exclusion criteria were a tumor length of more than 13 cm, tumor growth within 2 cm of the upper esophageal sphincter, a fistula between the esophagus and respiratory tree, and previous metal stent placement. Patients who were unfit to undergo conscious sedation were also excluded. Stent placement was performed in two hospitals, the Erasmus MC University Medical Center Rotterdam, the Netherlands (n=120), and the Istituto

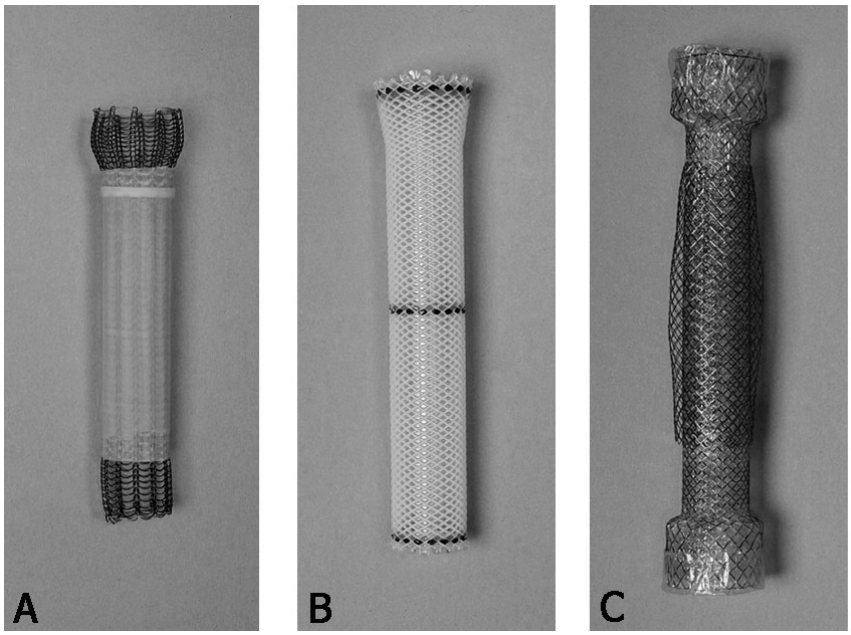

Figure 1. Stents that were used in this trial: Ultraflex stent (a), Polyflex stent (b), and Niti-S stent (c)

Clinico Humanitas, Milan, Italy (n=5). The study was approved by the Institutional Review Board of both hospitals.

For randomization, patients were stratified for location of the tumor (esophagus or gastric cardia), radiation and/or chemotherapy prior to treatment, and center. Randomization was performed by the Trial Office of the Department of Oncology, Erasmus MC Rotterdam, using a computer-generated allocation protocol.

Stents and stent placement procedure

Patients were treated with an Ultraflex stent, Polyflex stent or Niti-S stent (Figure 1). The Ultraflex stent (Boston Scientific, Natick, USA) consists of a knitted nitinol wire tube and has a polyurethane layer which covers the midsection of the stent extending to within 1.5 cm of either end of the stent. The stent has a proximal flare of 23 mm and a body diameter of 18 mm. It is available in three lengths: 10, 12 and 15 cm. The stent can be deployed gradually either from the proximal to distal end or vice versa. It is delivered in a compressed form inside an introducer sheath. The Polyflex stent (Rüsch AG, Kernen, Germany) is a silicone device with an encapsulated monofilament braid made of polyester. The meshes are completely covered by a silicone layer with a smooth inner surface and a more structured outer surface. The edges of the monofilaments are protected with silicone to avoid impaction and/or tissue damage at the proximal and distal ends. The stent has a proximal flare of 23 mm and a body

diameter of 18 mm. It is available in three lengths: 9, 12 and 15 cm. The stent needs to be loaded in the introducer sheath prior to placement. This introduction device has a diameter of 13 mm. The Niti-S stent (Taewoong Medical, Seoul, Korea) has a double layer configuration over its entire length, consisting of an inner polyurethane layer over its complete length and an outer uncovered nitinol wire. The stent flares to 26 mm at its proximal and distal ends with a body diameter of 18 mm. It is available in three lengths: 9, 12 and 15 cm. The stent is delivered in a compressed form inside an introducer sheath.

During stent insertion, all patients were consciously sedated with midazolam (DormicumR, Roche Nederland BV, Mijdrecht, the Netherlands). If tumor obstruction did not allow passage of a standard endoscope, the tumor was either dilated to a maximum of 12 mm by a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC, USA), or, in most cases, the standard diameter (8.9 mm) endoscope (GIF-Q160; Olympus B.V., Zoeterwoude, the Netherlands) was changed for a small diameter (5.9 mm) endoscope (GIF-XP160; Olympus B.V.). The upper and lower tumor margins were marked with sclerotherapy needle-injected radiographic contrast material. The stents were advanced over a guidewire into the esophagus. During and following stent placement, deployment of the stent was endoscopically and radiographically assessed. A stent, which was 2-4 cm longer than the stricture, was chosen to allow for a 1-2 cm extension above and below the proximal and distal tumor shoulder. A proton pomp inhibitor (PPI) was prescribed to all patients of whom the distal end of the stent was positioned across the gastro-esophageal (GE) junction to prevent GE reflux after the procedure.

Study endpoints

The primary outcome of the study was recurrent dysphagia. Secondary outcomes included technical and functional (dysphagia score, WHO performance score) outcome, complications, and survival.

Recurrent dysphagia was defined as occurrence of tissue in- or overgrowth, stent migration and food obstruction. Technical outcome was defined as ease of placement of the stent at the desired location. Dysphagia was scored as: 0 = ability to eat a normal diet; 1 = ability to eat some solids; 2 = ability to eat some semisolids only; 3 = ability to swallow liquids only; 4: complete dysphagia (6). Major complications were defined as life-threatening or severe complications, such as perforation, hemorrhage, fistula, aspiration-pneumonia and severe pain, whereas minor complications were defined as not life-threatening or moderately severe complications, such as mild pain and gastro-esophageal reflux. Survival included 30-day mortality and long term survival.

Follow-up

Patients were evaluated before stent placement, at 14 days and one month after placement, and then monthly until death. For patients still alive at the end of the study (October 31,

2006), follow-up was at least six months. Evaluations were performed by scheduled telephone calls to patients, and included the following items: 1) ability to eat and/or swallow (dysphagia score); 2) general health as assessed by the WHO performance score (graded as: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time; 4 = 100% bedridden); and 3) specific symptoms such as pain, heartburn, regurgitation, and weight loss. If indicated, for example in case of complications or recurrent dysphagia, patients were seen for evaluation and treatment. All evaluation items were recorded in a case record form.

Statistics

We calculated that for the primary endpoint of the study, i.e., a difference in recurrent dysphagia in favor of at least one of the newer stent designs (Polyflex stent or Niti-S stent), three groups of 39 patients each would be sufficient to detect a reduction in recurrence of dysphagia by at least 40% of that found with Ultraflex stents as was found in previous studies (3, 7, 8) (Ultraflex stent: 40% vs. Polyflex stent: 21% vs. Niti-S stent: 12 %), with a 2-sided α=5% and power of 80%.

All analyses were performed on an intention-to-treat basis. Patients were compared for the following baseline characteristics: age, gender, dysphagia score before stent placement, WHO performance score before treatment, tumor length, tumor location, histology, dilation before stent placement, and prior radiation and/or chemotherapy. Outcome included dysphagia score after stent placement, WHO performance score after placement, complications, recurrent dysphagia and survival (30-day and long term).

Results were expressed as means ± standard deviation (SD) and as medians with interquartile range (IQR), if appropriate; long term survival was expressed as median survival. The chi-square test was used for categorical variables. Complications and recurrent dysphagia between the three groups were compared with Kaplan-Meier and log rank tests to adjust for time of occurrence of the event and survival differences. The risk of developing complications or recurrent dysphagia was calculated using Cox regression analysis with prior radiation and/or chemotherapy and chemotherapy after stent placement as covariates. Dysphagia scores at 4 weeks after stent placement were analyzed using covariance analysis with dysphagia score at baseline taken as covariate. Survival of the three groups was calculated and compared using Kaplan-Meier curves and the log rank test. A p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

The patient groups were similar with respect to clinical characteristics (Table 1). In approximately 20% of patients, the malignant stricture was located in the gastric cardia, whereas in the other patients the tumor was located in the esophagus. Approximately one-third of the patients had undergone radiation and/or chemotherapy prior to stent placement. There were no differences in total stent length between the three patient groups, however, corrected for the part of the stent that was covered, Ultraflex stents were shorter ($p<0.001$). In addition, no

Table 1. Clinical characteristics of 125 patients treated with an Ultraflex stent, Polyflex stent or Niti-S stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

	Ultraflex stent n=42	**Polyflex stent n=41**	**Niti-S stent n=42**
Age; years; mean ± sd	69 ± 13	70 ± 10	65 ± 12
Gender; no. of patients (%)			
Male	28 (67)	28 (68)	30 (71)
Female	14 (33)	13 (32)	12 (29)
Median dysphagia score before treatment (IQR*)	3 (1)	3 (0)	3 (0)
Median WHO performance score before treatment (IQR)	1 (2)	1 (2)	1 (2)
Tumor length; cm; mean ± sd	8.1 ± 3	7.5 ± 2	7.5 ± 3
Stent length; cm; mean ± sd			
- total	12 ± 2	11 ± 2	12 ± 2
- covered part only#	9 ± 2	11 ± 2	12 ± 2
Ratio stent /tumor length; cm ± sd			
- total	1.6 ± 0,4	1.6 ± 0.3	1.7 ± 0.7
- covered part only#	1.2 ± 0,3	1.6 ± 0.3	1.7 ± 0.7
Location of tumor; no. of patients (%)			
Esophagus	35 (83)	33 (81)	35 (83)
- mid esophagus	12	7	10
- distal esophagus	23	26	25
Gastric cardia	7 (17)	8 (19)	7 (17)
Tumor histology; no. of patients (%)			
Adenocarcinoma	30 (73)	27 (66)	28 (68)
Squamous cell carcinoma	11 (27)	14 (34)	12 (30)
Other	0 (0)	0 (0)	1 (2)
Prior radiation and/or chemotherapy; no. of patients (%)			
Total	14 (33)	12 (29)	11 (26)
Chemotherapy	8 (19)	7 (17)	7 (17)
Radiation	3 (7)	0 (0)	1 (2)
Radiation and chemotherapy	3 (7)	5 (12)	3 (7)

* IQR: Interquartile range; # $p<0.001$

differences in total stent length to tumor length ratios were found between the three stent types (p=0.37), whereas length of the covered part of the stent to length of the tumor ratios were also lower for Ultraflex stents (p<0.001).

Recurrent dysphagia

Recurrent dysphagia occurred more frequently in patients with an Ultraflex stent (p=0.03), which was caused by tissue in- or overgrowth, stent migration, and/or food obstruction (Table 2). Tissue in- or overgrowth occurred more frequently with Ultraflex stents compared to Polyflex stents or Niti-S stents (n=13 (31%) vs. n=4 (10%) vs. n=10 (24%), respectively), and was observed after a median of 79 days after stent placement. Tissue in- or overgrowth was in the majority of patients (24/27 (89%)) treated by placement of a second stent.

Stent migration occurred more frequently in patients with a Polyflex stent (n=12 (29%)) (Figure 2a) compared to Ultraflex stents (n=7 (17%)) and Niti-S stents (n=5 (12%)). In 5/12 patients with a Polyflex stent, the stent migrated proximally, and in 7/12 patients stent migration was distally. None of the Ultraflex stents and Niti-S stents migrated proximally. Stent migration was mainly treated with a second stent (15/24; 63%) or repositioning of the stent (4/24; 17%) (Figure 2b). One patient developed abdominal pain after placement of a Niti-S stent. Repeat endoscopy did not reveal a stent in the esophagus and an additional X-ray showed that the stent had migrated to the small bowel. As the stent caused obstruction

Table 2. Recurrent dysphagia in 125 patients given a Ultraflex stent, Polyflex stent or Niti-S stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or esophago-gastric junction

	Ultraflex stent n=42	**Polyflex stent n=41**	**Niti-S stent n=42**	**p-value***
Recurrent dysphagia; total no. of patients (%)	33 in 22 pts (52)	18 in 15 pts (37)	17 in 13 pts (31)	0.03
	33 in 22 pts (52)	18 in 15 pts (37)		0.42
	33 in 22 pts (52)		17 in 13 pts (31)	<0.01
		18 in 15 pts (37)	17 in 13 pts (31)	0.06
- Tissue growth; no. of patients (%)	15 in 13 pts (31)	4 in 4pts (10)	11 in 10 pts (24)	0.09
	15 in 13 pts (31)	4 in 4pts (10)		0.04
	15 in 13 pts (31)		11 in 10 pts (24)	0.16
		4 in 4pts (10)	11 in 10 pts (24)	0.49
- Stent migration; no. of patients (%)	7 in 7 pts (17)	12 in 12 (29)	5 in 5 (12)	0.01
	7 in 7 pts (17)	12 in 12 (29)		0.07
	7 in 7 pts (17)		5 in 5 (12)	0.39
		12 in 12 (29)	5 in 5 (12)	<0.01
- Food bolus impaction; no. of patients (%)	11 in 10 pts (24)	2 in 2 pts (5)	1 in 1 pt (2)	<0.01
	11 in 10 pts (24)	2 in 2 pts (5)		0.04
	11 in 10 pts (24)		1 in 1 pt (2)	<0.01
		2 in 2 pts (5)	1 in 1 pt (2)	0.40

* Log rank test for time to first event of recurrent dysphagia

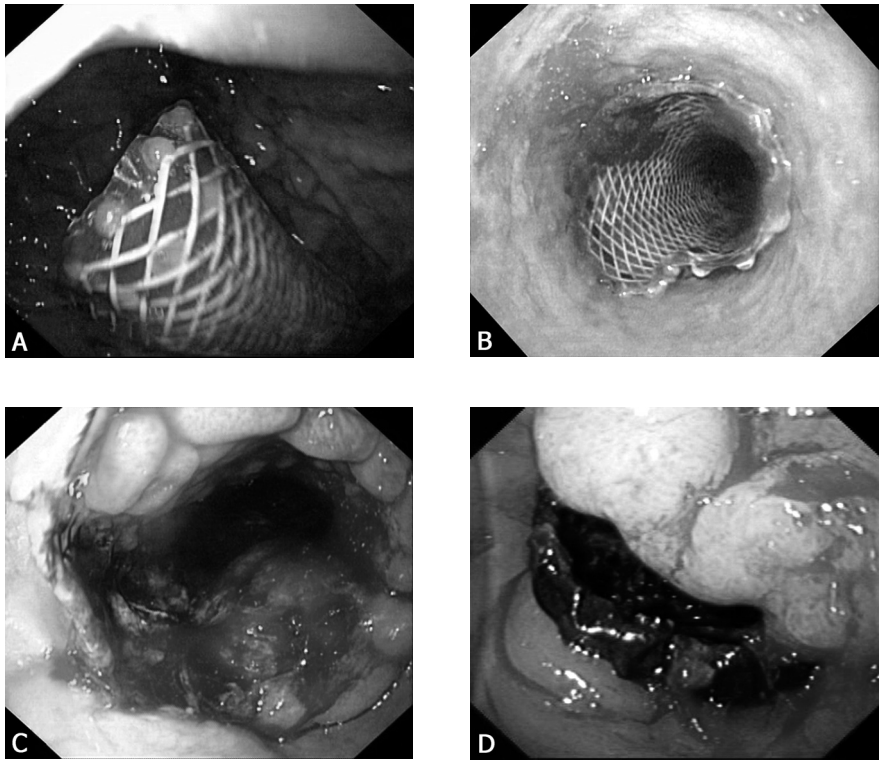

Figure 2. Stent migration with a Polyflex stent (a), which was endoscopically repositioned (b). Nontumoral tissue in- and overgrowth with an Ultraflex stent (c) and tumoral tissue overgrowth with a Niti-S stent (d)

and could not be retrieved endoscopically with double-balloon enteroscopy, the stent was surgically removed. The patient received another stent type because of increasing dysphagia. At the end of the study, this patient was still alive. Stent migration was observed in 8/24 (3 with an Ultraflex stent, 1 with a Polyflex stent and 4 with a Niti-S stent; p=0.41) patients who additionally received chemotherapy following stent placement. More patients with an Ultraflex stent underwent upper endoscopy for cleansing of the stent because of food obstruction than patients with a Polyflex stent or Niti-S stent (n=10 (24%) vs. n=2 (5%) vs. n=1 (2%), respectively; p=0.002). Additional statistical analysis showed no association between food obstruction and tumor/tissue in- or overgrowth for each of the stent types.

Two months after stent placement, all patients were invited to undergo upper endoscopy to investigate whether evidence of tumoral or nontumoral tissue in- or overgrowth could be detected. In total, 33/125 patients (9 with an Ultraflex stent, 11 with a Polyflex stent and 13 with a Niti-S stent) agreed. Twenty-seven patients refused to undergo upper endoscopy, whereas 26 patients were deemed unfit and 25 were already deceased at that time. In 15/33 (45%) patients (all three stents n=5), evidence of tissue in- or overgrowth at the proximal end of the stents was observed. Three (20%) of these patients also had symptoms of dys-

Table 3. Outcome and survival in 125 patients treated with an Ultraflex stent, Polyflex stent or Niti-S stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

	Ultraflex stent n=42	Polyflex stent n=41	Niti-S stent n=42	p-value
Technical success; no. of patients (%)	42 (100)	34 (83)	40 (95)	0.008
Dilation before treatment; no. of patients (%)	4 (10)	5 (12)	6 (14)	0.80
Median dysphagia score 4 weeks after treatment (IQR*)	0 (1)	1 (2)	0 (1)	0.07
Median WHO performance score 4 weeks after treatment (IQR)	1 (2)	1 (2)	1 (1)	0.31
Chemotherapy after treatment; no. of patients (%)	7 (17)	2 (5)	15 (36)	0.002
30-day mortality; no. of patients (%)	2 (5)	7 (17)	2 (5)	0.07
Median survival in days	132	102	159	0.13
Still alive; no. of patients (%)	5 (12)	6 (15)	11 (26)	0.19
Cause of death; no. of patients (%)				0.49
Stent-related	1 (2)	2 (5)	-	
Tumor progression	35 (84)	33 (80)	30 (72)	
Not related to tumor	1 (2)	-	1 (2)	

* IQR: Interquartile range

phagia and a second, but other stent was placed. Following additional stent placement, the dysphagia score improved. In all patients, biopsies were taken at the upper and lower end of the stent in case tissue growth was observed. Nontumoral tissue in- or overgrowth was found in 3/6 (50%) patients with an Ultraflex stent (Figure 2c), in 4/5 (80%) patients with a Polyflex stent, and in 3/4 (75%) patients with a Niti-S stent, whereas the remaining patients had tumoral tissue in- or overgrowth (Figure 2d). None of the patients with nontumoral tissue in- or overgrowth was symptomatic.

Outcome and survival

Stent placement was technically successful in all patients with an Ultraflex stent, in 34/41 (83%) patients with a Polyflex stent and in 40/42 (95%) patients treated with a Niti-S stent (p=0.008) (Table 3). Reasons for technical difficulties were too proximal (Polyflex stent n=4) or too distal stent placement (Polyflex stent n=3; Niti-S stent n=2) as noticed immediately after the procedure. In six patients, the stent was successfully repositioned with a grasping forceps. In two patients, the Polyflex stent was again loaded in the introducer sheath and placed, while in another patient randomized to a Polyflex stent, a second, but other stent type was placed.

At 4 weeks after stent placement, the dysphagia score had improved from a median of 3 (liquids only) to 1 (ability to eat some solid food) (Table 3). We found no significant differences in the degree of improvement between the three patient groups over 4 weeks time (p=0.22).

At 4 weeks, no differences in WHO performance score were observed (p=0.31). Following stent placement, 24/125 (19%) patients, mainly with Niti-S stents (n=15) or Ultraflex stents (n=7), received additional palliative chemotherapy and were treated with cisplatin and paclitaxel (Table 3). After six courses of chemotherapy, the tumor was considered to be resectable in 5 patients and surgery with curative intent was performed.

Median survival was 132 days in patients with an Ultraflex stent, 102 days in those with a Polyflex stent, and 159 days in those with a Niti-S stent (p=0.13). Twenty-two of 125 (18%) patients were still alive at the end of follow-up of at least 6 months. The majority of deceased patients (98/103; 95%) died from tumor progression, whereas three patients, two with a Polyflex stent and one with an Ultraflex stent, died from stent-related complications (Table 3).

Complications

Complications occurred in 9 (21%) patients with an Ultraflex stent, in 10 (24%) with a Polyflex stent, and in 9 (21%) with a Niti-S stent (Table 4). Of the early (≤ 7 days) major complications, perforations were seen in two patients treated with a Polyflex stent. One of these patients died from septic complications. In the other patient, a palliative resection was performed because of ongoing leakage in spite of seemingly adequate stent placement. Late (> 7 days) major complications consisted predominantly of hemorrhage (n= 11). Hemorrhage occurred more frequently with Ultraflex stents (n=5) and Polyflex stents (n=5). Five patients with hemorrhage were successfully treated with external beam radiation therapy (EBRT), and three patients required at least one blood transfusion. Three patients were treated with a combina-

Table 4. Complications in 125 patients treated with an Ultraflex stent, Polyflex stent or Niti-S stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

	Ultraflex stent n=42	Polyflex stent n=41	Niti-S stent n=42	p-value#
	No. of patients (%)			
Total complications	12 in 9 pts (21)	11 in 10 pts (24)	10 in 9 pts (21)	0.89
Major complications	9 in 9 pts (21)	8 in 8 pts (20)	5 in 5 pts (12)	0.48
≤ 7 days				
perforation	-	2	-	
severe pain	1	-	2	
fever	1	-	-	
aspiration pneumonia	-	1	-	
hemorrhage	-	-	1	
> 7 days				
hemorrhage	5	5	1	
fistula	2	-	1	
Minor complications	3 in 3 pts (7)	3 in 3 pts (7)	5 in 4 pts (10)	0.94
mild retrosternal pain	2	1	2	
gastro-esophageal reflux	1	2	3	

Log rank test for time to first complication

tion of EBRT and blood transfusion, whereas one of these patients was additionally treated with endoscopic argon plasma coagulation. No patient died as a consequence of hemorrhage. Three patients, two with an Ultraflex stent and one with a Niti-S stent, developed an esophagorespiratory fistula, which was successfully sealed with a second stent in all patients. However, one of these patients died from progressive respiratory failure. Another patient, treated with a Polyflex stent, died from progressive respiratory failure following aspiration pneumonia.

Minor complications, mainly retrosternal pain and gastroesophageal reflux, were seen in 3 (7%) patients with an Ultraflex stent, in 3 (7%) with a Polyflex stent, and in 4 (10%) with a Niti-S stent (Table 4). The pain was stent-related in all patients and required treatment with analgesics, which was in most cases for a short (≤ 1 week) period.

We performed a univariate analysis of patients previously treated with radiation and/or chemotherapy or subsequently treated with chemotherapy. This analysis showed that the occurrence of complications (Hazard Ratio (HR) 1.50, 95%CI 0.69-3.24) and recurrence of dysphagia (HR 1.57, 95%CI 0.86-2.86) were not associated with prior radiation and/or chemotherapy. In addition, complications (HR 0.53, 95%CI 0.18-1.55) and recurrent dysphagia (0.74, 95%CI 0.38-1.42) was also not associated with chemotherapy following stent placement.

DISCUSSION

In this randomized trial, we found that Ultraflex stents, Polyflex stents and Niti-S stents were equally effective and safe for the palliation of dysphagia from inoperable or recurrent carcinoma of the esophagus or gastric cardia. Technical problems during stent placement were more frequently observed with Polyflex stents than with Ultraflex stents and Niti-S stents (p=0.008). Recurrent dysphagia however occurred more frequently with Ultraflex stents than with the newer stent types (p=0.03) (Table 2).

Stent placement was technically successful in the majority (116/125 (93%)) of patients (Table 3). Stents were however positioned too proximally or too distally in seven patients with a Polyflex stent and in two patients with a Niti-S stent, as became evident immediately after stent insertion. In case of Polyflex stents, this was caused by uncontrollable stent deployment at its final stage, when the last 20-40% of the stent is released from the introduction catheter. At that stage, the stent tends to jump in an unpredictable way from the sheath (3, 9). We were successful in repositioning the stent in 8/9 patients, whereas in one patient an alternative stent type was placed.

Recurrent dysphagia was caused by tissue in- or overgrowth, stent migration, and food obstruction (Table 2). Tissue in- or overgrowth at the stent end can be due to non-malignant hyperplastic tissue growth (Figure 2c), or progressive tumor growth (Figure 2d). It has been demonstrated that tissue overgrowth from non-malignant obstructive tissue is more

likely to occur in patients with a prolonged survival. Mayoral et al. (4) showed the presence of nontumoral tissue at the ends of different types of partially and fully covered stents in 32% of patients after a mean interval of 22 weeks. In our study, tissue in- or overgrowth was observed in 16/33 (48%) patients who had undergone a scheduled upper endoscopy for this indication two months after stent placement. Only three of these patients had symptoms of recurrent dysphagia. Biopsies confirmed in 10/16 (62%) patients the presence of nontumoral tissue in- or overgrowth. Symptomatic tissue in- or overgrowth occurred more frequently with Ultraflex stents (31%) and Niti-S stents (24%) compared to Polyflex stents (10%) (Table 2). This is not clearly different from the rather large range of reported tissue in- or overgrowth rates observed in other studies, varying between 3-31% (4, 7, 10, 11). Although not shown by the 2-month biopsy results in our study, which showed an equal distribution of tumoral and nontumoral tissue in- or overgrowth between the different stents types, it might well be that the material of the Polyflex stent, made of polyester and silicone, is able to prevent hyperplastic tissue formation in the long term, in contrast to the nitinol braiding of both the Ultraflex stent and Niti-S stent. Another explanation for the observed differences could be that both stent ends of the Ultraflex stent are uncovered over a distance of 1.5 cm, allowing tissue to project into the esophageal lumen. Moreover, the ratio between the covered part of the stent and the total tumor length was shorter for Ultraflex stents than for Polyflex stents and Niti-S stents in this study (Table 1). This latter factor may additionally have contributed to the occurrence of tumoral tissue in- or overgrowth with Ultraflex stents. We therefore suggest that if partially covered stents are used, the choice for stent length should also be determined by the length of the covered part of the stent.

Stent migration is still a frequently occurring problem, particularly for distally located tumors (12). This cause of recurrent dysphagia was most frequently seen with Polyflex stents (29%) (Figure 2a-b) compared to Ultraflex stents (17%) and Niti-S stents (12%) (Table 2). The design of the stent is probably important in reducing stent migration. The Ultraflex stent has uncovered proximal and distal segments, which, as has been stated previously, allows the normal mucosa above and below the tumor to project into the stent lumen. In the Dutch SIREC study, a similar stent migration rate was found with Ultraflex stents, i.e., 17% (18/108 patients) (7). The Niti-S stent was specifically designed to reduce, if not eliminate, stent migration with the combination of a flare to 26 mm at both ends, and an outer uncovered nitinol wire over a polyurethane layer for embedment in the esophageal wall. In a previous case series, stent migration was observed in 3/42 (7%) patients treated with a Niti-S stent (8). The relatively high migration rate of the Polyflex stent was not surprising, because the Polyflex stent is completely covered by a relatively smooth silicone membrane. Nonetheless, reported results for migration with Polyflex stents are conflicting. In a study by Dormann et al. (3), migration was observed in only 6% (2/33) of patients with malignant dysphagia. In contrast, in a study from Rome, a comparable migration rate of 25% (4/16) was found (13).

For food obstruction of the stent, endoscopic cleansing was an effective treatment. Although both food obstruction and tissue in- or overgrowth occurred more frequently with Ultraflex stents (24%) than with Polyflex stents (5%) and Niti-S stents (2%), no association was found between these two causes of recurrent dysphagia. Prevention is important and consists of providing clear eating instructions to patients, specifically with regard to thorough chewing of food and drinking effervescent drinks between bites and after meals to flush the stent. Although all patients received a brochure with instructions on eating, food obstruction still occurred in 13/125 (10%) of patients.

Complications were observed in 28/125 (22%) patients with no differences between patients treated with an Ultraflex stent, Polyflex stent or Niti-S stent (Table 4). Perforation occurred in two patients during introduction of a Polyflex stent, resulting in the death of one patient, and surgery in the other patient. These perforations may have been caused by the size of the introduction system. The applicator, in which the stent is loaded prior to stent placement, has a diameter of 13 mm and is rather rigid. In addition, the stent seems to be less suitable for angulated strictures because the distal dilator is rather short. The inappropriate forced transmission of such an introduction sheath may complicate its passage across such strictures. A common late complication was the occurrence of late hemorrhage. This was also previously seen in the SIREC study (7). Hemorrhage in that study was observed in 14/108 (13%) patients treated with a stent, but only in 5/101 (5%) patients treated with brachytherapy ($p=0.05$). Whether the radiation effect of brachytherapy had a protective effect on bleeding from the tumor through tumor reduction or a haemostatic effect on the tumor vasculature, or that the expanding force of a stent increase bleeding risk remained unclear. Although some studies have suggested that an increased risk of complications is associated with previous radiation and/or chemotherapy (14), this could not be confirmed in the current study, nor in other series (15-17).

The present study demonstrates that all three stents are safe and offer the same degree of palliation at the same level of safety in patients with inoperable or recurrent carcinoma of the esophagus or gastric cardia. We previously found that brachytherapy was favorable over (Ultraflex) stent placement with regard to long-term relief of dysphagia and the occurrence of fewer complications (7). The presently available new-generation stents probably offer no improvement for these two effects. Based on our findings, we conclude that Polyflex stents seem the least preferable in this patient group, as placement of this device is technically demanding and associated with a high rate of stent migrations. We recommend the use of Niti-S stents or Ultraflex stents that are long enough to cover the full tumor length in patients with dysphagia from esophageal or gastric cardia cancer, particularly in patients with a calculated life expectancy of less than 3 months (18).

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5C

Effect of stent size on complications and recurrent dysphagia in patients with esophageal or gastric cardia cancer

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ABSTRACT

Background: Stents are commonly used for the palliation of dysphagia from esophageal or gastric cardia cancer. A major drawback of stents is the occurrence of recurrent dysphagia. Large-diameter stents have been introduced for the prevention of migration but may be associated with more complications.

Objective: To compare small- and large-diameter stents for improvement of dysphagia, complications and recurrent dysphagia.

Design: Evaluation of 338 prospectively followed patients with dysphagia from obstructing esophageal or gastric cardia cancer who were treated with an Ultraflex stent (n=153), a Gianturco Z-stent (n=89), or a Flamingo Wallstent (n=96) of either a small-diameter (n=265) or large-diameter (n=73) in the period 1996 to 2004.

Setting: Single academic center.

Patients: Patients with an inoperable malignant obstruction of the esophagus or gastric cardia, or recurrent dysphagia after prior radiation with curative or palliative intent for esophageal cancer.

Interventions: Stent placement.

Main outcome measurements: Dysphagia score (on a scale from 0, no dysphagia, to 4, complete dysphagia), complications and recurrent dysphagia. Analysis was by chi-square test, log-rank test, and Cox regression analysis.

Results: Improvement in dysphagia was similar between patients with a small- or a large-diameter stent (p=0.35). The occurrence of major complications, such as hemorrhage, perforation, fistula, and fever was increased in patients with a large-diameter Gianturco Z-stent compared with those treated with a small-diameter stent (4 [40%] vs. 16 [20%]; adjusted Hazard Ratio [HR] =5.03 [95%CI 1.33-19.11]), but not in patients with a large-diameter Ultraflex stent or Flamingo Wallstent. Moreover, minor complications, particularly pain, were associated with prior radiation and/or chemotherapy in patients with a large- or a small-diameter Gianturco Z-stent (HR=4.27 [95%CI 1.44-12.71]), but not in those with an Ultraflex stent or a Flamingo Wallstent. Dysphagia from stent migration, tissue overgrowth and food bolus obstruction reoccurred more frequently in patients with a small-diameter than in those with a large-diameter stent (Ultraflex stent: 54 [42%] vs.3 [13%]; adjusted HR=0.16 [95%CI 0.04-0.74], Gianturco Z-stent: 21 [27%] vs.1 [10%]; adjusted HR=0.97 [95%CI 0.11-8.67] and Flamingo Wallstent: 21 [37%] vs.6 [15%]; adjusted HR=0.40 [95%CI 0.03-4.79].

Limitations: Nonrandomized study design.

Conclusion: Large-diameter stents reduce the risk of recurrent dysphagia from stent migration, tissue overgrowth or food obstruction. Increasing the diameter in some stent types may, however, increase the risk of stent-related complications to the esophagus.

INTRODUCTION

Despite recent advances in the treatment of esophageal cancer (1), still 50-60% of patients have incurable disease at presentation. For these patients, palliative therapy to relieve dysphagia is the only treatment option available. Placement of a partially or fully covered stent is a commonly used method for the palliation of malignant dysphagia (2). The stent cover prevents ingrowth of tumor tissue through the metal mesh, which has been reported to occur in more than 25% of patients treated with an uncovered stent (3).

It has been suggested that covered stents are more likely to migrate than bare stents. In a recently performed prospective study in patients with dysphagia from inoperable cancer of the esophagus or gastric cardia, stent migration was observed in 18 (17%) of 108 patients treated with a covered stent. This necessitated a reintervention in the majority of patients (4). To overcome the problem of stent migration, larger-diameter stents have been introduced. The extra pressure on the esophageal wall exerted by large-diameter stents may, however, be associated with an increased risk of complications, in particular, pain (5).

In the present study, we compared small- and large-diameter stents for the risk of developing complications and recurrent dysphagia in a large cohort of patients with dysphagia from esophageal cancer and treated with different stent types

PATIENTS AND METHODS

Patients

At the Erasmus MC Rotterdam, from January 1996 to December 2004, 556 patients were treated with a metal stent in the esophagus or gastric cardia. Data from these patients were collected in a prospective database. Informed consent of patients to analyze this information is not needed in The Netherlands. Patients were included if they had an inoperable malignant obstruction of the esophagus or gastric cardia, or recurrent dysphagia after prior radiation with curative or palliative intent for esophageal cancer. A tumor was considered inoperable if the patient had distant metastases, local tumor infiltration in neighboring organs, and/or a poor health from concomitant disease. Exclusion criteria were tumor growth within 2 cm of the upper esophageal sphincter, a fistula between the esophagus and respiratory tree, recurrent tumor after esophagectomy or gastrectomy, previous metal stent placement, and benign strictures. Patients with an incomplete follow-up and patients who were unfit to undergo conscious sedation were also excluded. In total, 338 patients fulfilled the inclusion criteria.

All patients were evaluated before stent placement and at 4-weeks intervals after stent placement until death. Evaluations were performed by scheduled home visits of a research nurse or telephone calls to the patient and/or the patients' general practitioner. They included

the following items: 1) ability to eat and/or swallow (graded as follows: 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 grade 4: complete dysphagia); and 2) specific symptoms, such as pain, heartburn, regurgitation, and weight loss. When indicated, for example, in case of complications or recurrent dysphagia, patients were seen for evaluation and treatment. If a patient was referred to another center for a complication or recurrent dysphagia, then relevant clinical information was obtained from that hospital.

Placement of stents

During stent insertion, all patients were consciously sedated with midazolam (Dormicum®, Roche Nederland BV, Mijdrecht, the Netherlands). If it was impossible to pass the tumor with an endoscope, the stricture was dilated to a maximum of 12 mm by a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC, USA). The upper and lower tumor margins were marked with sclerotherapy needle-injected radiographic contrast material. The stents were advanced over a guidewire into the esophagus. The stents were mostly deployed under fluoroscopic monitoring; however in some instances, the stent was deployed under endoscopic view. A stent of 2-4 cm longer than the stricture was chosen to allow for a 1-2 cm extension above and below the proximal and distal tumor shoulder.

Three types of stent were used:

- Partially covered Ultraflex stents (Boston Scientific, Natick, USA) in lengths of 10,12 and 15 cm, and diameters of 23 (proximal)/18 (distal) mm (small) and 28 (proximal)/23 (distal) mm (large) (Figure 1). The stent is uncovered at both ends over a distance of 1.5 cm;
- Fully covered Gianturco Z-stent (Wilson-Cook Europe, Bjaeverskov, Denmark) in lengths of 10, 12 and 14 cm, and diameters of 18 mm (small) or 22 mm (large) at its midsection with both ends flared to a diameter of 25 mm.
- Partially covered Flamingo Wallstent (Boston Scientific, Natick, USA) in lengths of 12 cm (small: proximal diameter 24 mm and distal diameter 16 mm) and 14 cm (large: proximal diameter 30 mm and distal diameter 20 mm) (Figure 1). The stent is uncovered at both ends over a distance of 1.5 cm.

Statistical analysis

The following clinical characteristics were considered: age, gender, dysphagia score before stent placement, tumor length, tumor location, histology, dilation before stent placement, type of stent, stent length, prior radiation and/or chemotherapy, total stent length to tumor length ratio and total length of the stent that was covered to tumor length ratio. Outcome included the following: dysphagia score after stent placement, complications, recurrent dysphagia and mortality (30-day and long-term survival).

The results were expressed as means ± standard deviation (SD), and medians with interquartile range (IQR); long-term survival was expressed as median survival. Dysphagia scores

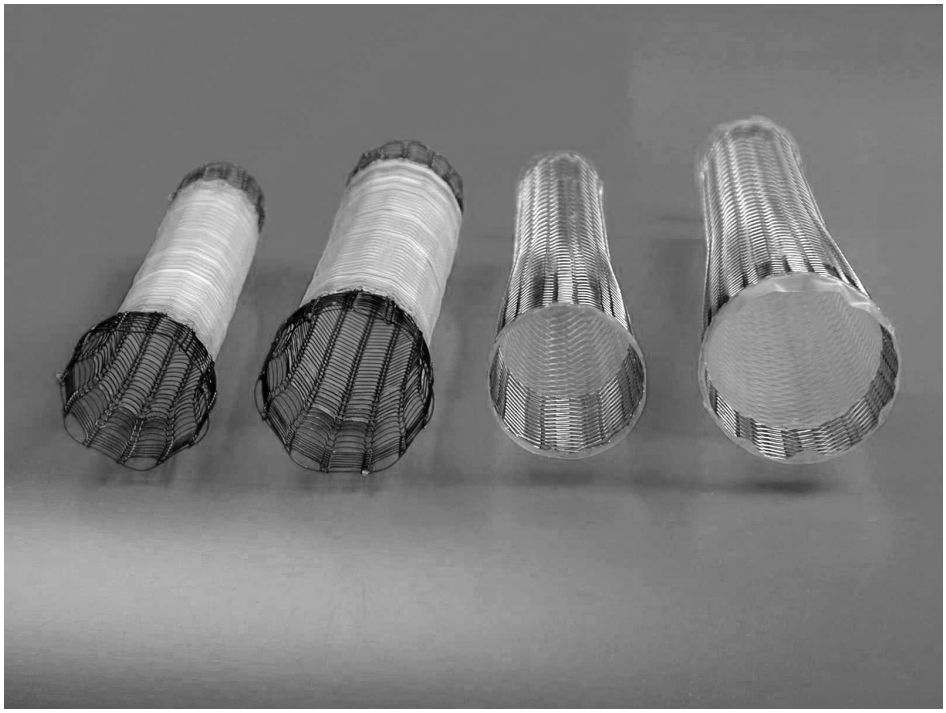

Figure 1. Two of the three stent types that were used in the present study, form left to right: small diameter and large diameter Ultraflex stent, and small diameter and large diameter Flamingo Wallstent

at 4 weeks after placement of small- or large-diameter stents were analyzed using covariance analysis with dysphagia score before treatment taken as covariate. The risk of developing complications or recurrent dysphagia was calculated using Cox regression analysis with age, tumor length, tumor location, prior radiation and/or chemotherapy, total length of the covered part of the stent and type of stent as covariates. These factors were included as confounders in a multivariable model. A p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

Clinical characteristics of the 338 patients treated with a small-diameter (n=265) or a large-diameter (n=73) stent and fulfilling the inclusion criteria are shown in Table 1. In approximately 20% of patients, the tumor was located in the gastric cardia, whereas, in the remainder, it was located in the esophagus. Large-diameter stents were more frequently placed in patients with a tumor located in the gastric cardia ($p<0.0001$). If the Flamingo

Table 1: Clinical characteristics of 338 patients treated with a small or large diameter stent for palliation of dysphagia because of inoperable carcinoma of the esophagus or gastric cardia

Characteristics	Small diameter stent n=265	Large diameter stent n= 73	p-value
Age; yrs (mean ± sd)	67 ± 12	69 ± 13	0.23
Gender; no. of patients (%)			0.99
- Male	189 (71)	52 (71)	
- Female	76 (29)	21 (29)	
Dysphagia score before treatment; median (IQR)*	3 (1)	3 (1)	0.70
Tumor length; cm (mean ± sd)	7.7 ± 3	7.9 ± 3	0.37
Stent length; cm (mean ± sd)			
- Total	12 ± 2	13 ± 1	0.001
- Covered part only	10 ± 2	10 ± 1	0.76
Ratio stent /tumor length; cm ± sd			
- Total	1.8 ± 0,6	1.9 ± 0.8	0.25
- Covered part only	1.4 ± 0,5	1.4 ± 0.6	0.88
Location of tumor; no. of patients (%)			<0.0001
- Esophagus	235 (89)	44 (60)	
mid esophagus	124	21	
distal esophagus	111	23	
- Cardia	30 (11)	29 (40)	
Tumor histology; no. of patients (%)			0.08
- Squamous cell carcinoma	101 (38)	16 (22)	
- Adenocarcinoma	149 (56)	51 (70)	
- Other	15 (6)	6 (8)	
Type of stent; no. of patients (%)			<0.0001
- Ultraflex stent	129 (49)	24 (33)	
- Gianturco Z-stent	79 (30)	10 (14)	
- Flamingo Wallstent	57 (21)	39 (53)	
Prior radiation and/or chemotherapy; no. of patients (%)			0.33
- Total	96 (36)	22 (30)	
- Chemotherapy	49 (22)	10 (14)	
- Radiation	10 (6)	5 (7)	
- Radiation and chemotherapy	37 (8)	7 (9)	

* IQR: Interquartile range

Wallstent was used, more often a large-diameter stent was inserted (p<0.0001). The total stent length was longer in patients treated with a large-diameter stent compared to patients with a small-diameter stent (p<0.001), however, corrected for the part of the stent that was covered, this difference was no longer present (p=0.76). In addition, no differences between small- and large-diameter stents were found for the ratios of total stent to tumor length (1.8 ± 0.6 vs. 1.9 ± 0.8; p=0.25), and total length of the covered part of the stent to tumor length (1.4 ± 0.5 vs. 1.4 ± 0.6; p=0.88).

Table 2: Outcome and survival of 338 patients treated with a small or large diameter stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

Characteristics	Small diameter stent n=265	Large diameter stent N=73	p-value
Dilation before treatment; no. of patients (%)	40 (15)	9 (12)	0.55
Dysphagia score 4 wks after treatment; median (IQR)*	1 (1)	0 (1)	0.35
30-day mortality; no. of patients (%)	32 (12)	15 (21)	0.07
Median survival in days	116	100	0.24
Cause of death; no. of patients (%)			0.06
- Stent-related	6 (2)	4 (6)	
- Tumor progression	231 (87)	54 (77)	
- Not related to tumor	27 (10)	11 (15)	

* IQR: Interquartile range

Outcome and survival

Metal stent placement was technically not successful in 16/338 (5%) patients. Technical failure was most frequently seen in patients treated with a small Gianturco Z-stent (13/16 (81%); small vs. large diameter: 12/13 vs. 1/13). In the majority of these patients, a second but other stent type was successfully inserted. Causes of technical failure included stent migration during placement (n=6), inadequate stent length (n=5), or other reasons (n=5).

The dysphagia score improved from a median of 3 (liquids only) to 0 (ability to eat a normal diet) in all patients 4 weeks after treatment ($p<0.001$) (Table 2). The degree of improvement was not different between patients with an Ultraflex stent, a Gianturco Z-stent, or a Flamingo Wallstent with either a small- or large-diameter stent ($p=0.35$) (Table 2). Median survival was 116 days in the group of patients with a small-diameter stent and 100 days in those with a large-diameter stent ($p=0.24$). The majority of patients (285/338 (84%)) died as a result of tumor progression. Ten (3%) patients died from a stent-related complication, with a trend towards more stent-related deaths in patients treated with a large-diameter stent ($p=0.06$) (Table 2).

Complications

Complications were observed in 96/265 (36%) patients with a small-diameter stent and in 29/73 (40%) patients with a large-diameter stent (Table 3). Major complications (hemorrhage (44), perforation (15), fistula (9), fever (8) and aspiration pneumonia (4)) occurred in 76/366 (22%) patients. The risk of major complications was not different between patients with a small- or a large-diameter stent (60 [23%] vs. 16 [22%]; adjusted HR=1.31 [95%CI 0.81-2.12]), however, major complications, such as hemorrhage, perforation, fistula and fever, occurred

Table 3: Complications and recurrent dysphagia of 338 patients treated with a small or large diameter Ultraflex stent, Gianturco Z-stent, or Flamingo Wallstent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

	Overall				Ultraflex stent			
Complications	**Small diameter n=265; no. of pts (%)**	**Large diameter n=73; no. of pts (%)**	**HR (95% CI) Univariate**	**HR (95% CI) Adjusted***	**Small diameter n=129; no. of pts (%)**	**Large diameter n=24; no. of pts (%)**	**HR (95% CI) Univariate**	**HR (95% CI) Adjusted***
Total complications	119 in 96 pts (36)	33 in 29 pts (40)	1.30 (0.85-1.97)	1.31 (0.81-2.12)	54 in 44 pts (34)	10 in 9 pts (38)	1.21 (0.59-2.49)	1.00 (0.43-2.34)
Major complications	64 in 60 pts (23)	16 in 16 pts (22)	1.14 (0.65-1.98)	1.35 (0.72-2.53)	34 in 33 pts (26)	5 in 5 pts (21)	0.85 (0.33-2.19)	0.85 (0.29-2.51)
- Hemorrhage	33	11			20	3		
- Perforation	11	4			4	1		
- Fistula	9	0			5	0		
- Fever	7	1			3	1		
- Aspiration pneumonia	4	0			4	0		
Minor complications	55 in 52 pts (20)	17 in 14 pts (19)	1.03 (0.57-1.86)	0.95 (0.47-1.90)	20 in 19 pts (15)	5 in 4 pts (17)	1.03 (0.34-3.10)	0.72 (0.19-2.74)
- Pain	31	14			10	4		
- Gastro-esophageal reflux	24	3			10	1		
Recurrent dysphagia	117 in 96 pts (36)	10 in 10 pts (14)	0.37 (0.19-0.72)	0.35 (0.17-0.73)	70 in 54 pts (42)	2 in 3 pts (13)	0.13 (0.03-0.54)	0.16 (0.04-0.74)
- Tissue overgrowth	47	5			19	1		
- Stent migration	39	2			27	0		
- Food bolus impaction	31	3			24	1		

* adjusted for age, tumor length, location tumor, prior radiation and/or chemotherapy, stent type, length of stent cover

(Table 3: continued)

	Gianturco Z-stent				Flamingo Wallstent			
Complications	**Small diameter n=79; no. of pts (%)**	**Large diameter n=10; no. of pts (%)**	**HR (95% CI) Univariate**	**HR (95% CI) Adjusted***	**Small diameter n=57; no. of pts (%)**	**Large diameter n=39; no. of pts (%)**	**HR (95% CI) Univariate**	**HR (95% CI) Adjusted***
Total complications	36 in 30 pts (38)	7 in 6 pts (60)	2.49 (1.01-6.12)	3.48 (1.29-9.42)	29 in 22 pts (39)	16 in 14 pts (36)	0.99 (0.51-1.95)	0.16 (0.03-1.01)
Major complications	17 in 16 pts (20)	4 in 4 pts (40)	2.98 (0.97-9.19)	5.03 (1.33-19.11)	13 in 11 pts (19)	7 in 7 pts (18)	1.06 (0.41-2.74)	0.54 (0.02-11.97)
- Hemorrhage	10	3			3	5		
- Perforation	3	1			4	2		
- Fistula	1	0			3	0		
- Fever	3	0			1	0		
- Aspiration pneumonia	0	0			2	0		
Minor complications	19 in 19 pts (24)	3 in 3 pts (30)	1.43 (0.42-4.83)	2.76 (0.68-11.26)	16 in 14 pts (25)	9 in 7 pts (18)	0.74 (0.30-1.83)	0.09 (0.01-0.74)
- Pain	10	3			11	7		
- Gastro-esophageal reflux	9	0			5	2		
Recurrent dysphagia	23 in 21 pts (27)	1 in 1 pts (10)	0.49 (0.07-3.65)	0.97 (0.11-8.67)	24 in 21 pts (37)	6 in 6 pts (15)	0.57 (0.23-1.42)	0.40 (0.03-4.79)
- Tissue overgrowth	15	1			13	3		
- Stent migration	5	0			7	1		
- Food bolus impaction	3	0			4	2		

* adjusted for age, tumor length, location tumor, prior radiation and/or chemotherapy, stent type, length of stent cover

more frequently in the subgroup of patients with a large-diameter Gianturco Z-stent compared with those treated with a small-diameter stent (4 [40%] vs. 16 [20%]; adjusted HR=5.03 [95%CI 1.33-19.11]). Hemorrhage occurred in 33 patients with a small-diameter stent and in 11 patients with a large-diameter stent. Nine patients with hemorrhage were successfully treated with radiation therapy, whereas 17 patients required at least one blood transfusion. Nine patients died as a consequence of hemorrhage. Because these patients were already in a poor medical condition because of progressive metastatic disease when hemorrhage occurred, no diagnostic procedures were performed. Perforation occurred in 11 patients with a small-diameter stent and in four patients with a large-diameter stent. In 9 (60%) of these patients, the perforation was caused by dilation of the stricture before stent placement and seen within the tumor. The perforation in these patients was successfully sealed by the inserted stent. In the remaining 6 patients, the perforation was a stent-related complication and most commonly observed at the proximal end of the stent. These patients underwent a conservative treatment, which included administration of antibiotics, nil per mouth and feeding through a nasoduodenal tube. One patient died from progressive respiratory failure as a consequence of perforation. Nine patients developed an esophagorespiratory fistula, which was successfully occluded by a second stent in all patients. The occurrence of major complications was not associated with age, tumor length or location, prior radiation and/or chemotherapy, stent type, or length of the covered part of the stent (Table 4).

Minor complications, mainly retrosternal pain and gastroesophageal reflux, were seen in 52 patients with a small-diameter stent and in 14 patients with a large-diameter stent (Table 3). The risk of developing minor complications was not different between patients with a small- or a large-diameter stent (52 [20%] vs. 14 [19%]; adjusted HR=0.95 [95% CI 0.47-1.90]). Multivariable analysis showed that treatment with a small- or a large-diameter Gianturco Z-stent (HR=2.83 [95%CI 1.15-6.98]) increased the risk of minor complications (Table 4). Pain following stent placement required, in less than half of patients, treatment with analgesics for a short (≤ 1 week; n=16), or prolonged (> 1 week; n=5) period. Remarkably, treatment with a large-diameter Flamingo Wallstent (HR=0.09 [95%CI 0.01-0.74]) and increasing the stent cover of the Flamingo Wallstent (HR=3.25 [95%CI 1.08-9.80]) also decreased the risk of minor complications.

Recurrent dysphagia

Recurrent dysphagia occurred in 106 (31%) patients and was caused by tissue overgrowth (n=52), stent migration (n=41), and food bolus impaction (n=34) (Table 3). In 29 (9%) patients, tissue overgrowth was observed at the proximal end of the stent (small diameter n=27; large diameter n=2), in 17 patients at the distal end (small diameter n=16; large diameter n=1) and in 3 patients at both the proximal and distal end of the stent (small diameter n=3; large diameter n=0). Recurrent dysphagia occurred less frequently with large-diameter stents than with small-diameter stents (96 [36%] vs. 10 [14%]; adjusted HR=0.35 [95%CI 0.17-0.73]) (Table 4).

This was because of a difference in stent migration (39 vs. 1; p=0.002), tissue overgrowth (47 vs. 5; p=0.02), and food bolus impaction (31 vs. 3; p=0.08) between small- and large-diameter stents. The observed difference between large- and small-diameter stents in terms of recurrent dysphagia was particularly seen with Ultraflex stents (large: 3 [13%] vs. small: 54 [42%]; adjusted HR=0.16 [95%CI 0.04-0.74]), but also, although to a lesser extent, with Gianturco-Z stents (large: 1 [10%] vs. small: 21 [27%]; adjusted HR=0.97 [95%CI 0.11-8.67]) and Flamingo Wallstents (large: 6 [15%] vs. small: 21 [37%]; adjusted HR=0.40 [95%CI 0.03-4.79]). Recurrence of dysphagia was not associated with age, tumor length or location, prior radiation and/or chemotherapy, stent type, or length of the covered part of the stent (Table 4).

DISCUSSION

This non-randomized comparison between small- and large-diameter stents demonstrates that endoscopic placement of large-diameter stents was associated with a lower frequency of recurrent dysphagia, from stent migration, tissue overgrowth and food bolus obstruction. Nonetheless, for some stent types, particularly the Gianturco Z-stent, increasing the stent size will likely result in more stent-related complications to the esophagus.

Migration has been suggested to occur more frequently with stents placed across the gastro-esophageal junction compared to stents placed for more proximal tumors (6). This is probably because, in this position, the distal part of the stent cannot fix itself into the wall, because it projects freely into the fundus of the stomach. The design of the stent may well play a role in reducing stent migration. The Flamingo Wallstent has a shift in the braiding angle between the proximal and the distal part of the stent, which allows the distal part of the stent to stretch in response to peristalsis (5). The Ultraflex stent and both versions of the Wallstent have proximal and distal uncovered segments, which allow the normal mucosa above and below the tumor to project into the stent lumen. The European version of the Z-stent is available with metal barbs on the outside of the stent to anchor it into the tumor (7).

The present study is the first to show that increasing the flange diameter (30 mm for the Flamingo Wallstent and 28 mm for the Ultraflex stent), and/or increasing the diameter of the mid-portion of the stent (22 mm for the Z-stent), is also an important factor in the prevention of stent migration. Not surprisingly, in 29 (40%) patients treated with a large-diameter stent, the tumor was located in the gastric cardia (Table 1). In many of these cases, there was preference for a large-diameter Flamingo Wallstent, because this stent was specifically design for this indication (5) (Table 1). Multivariable analysis, however, showed that recurrent dysphagia was not associated with tumor location, and the only factor that was associated with recurrence of dysphagia was stent diameter (Table 4).

It has been suggested that the increased expansion force exerted by large-diameter stents on the esophageal wall may cause more pressure-related complications, such as hemor-

Table 4. Multivariable model to adjust the relationship between large diameter stents and occurrence of major and minor complications, and recurrent dyspahagia in 338 patients treated with a small or large diameter stent for palliation of dysphagia due to inoperable carcinoma of the esophagus or gastric cardia

	Total complications				Major complications			
Characteristics	**Overall HR (95%CI)**	**Ultraflex stent HR (95%CI)**	**Gianturco Z-stent HR (95%CI)**	**Flamingo Wall stent HR (95%CI)**	**Overall HR (95%CI)**	**Ultraflex stent HR (95%CI)**	**Gianturco Z-stent HR (95%CI)**	**Flamingo Wall stent HR (95%CI)**
Diameter								
- Small	1	1	1	1	1	1	1	1
- Large	1.30 (0.80-2.11)	1.00 (0.43-2.34)	3.48 (1.29-9.42)	0.16 (0.03-1.01)	1.32 (0.70-2.50)	0.85 (0.29-2.51)	5.03 (1.32-19.11)	0.54 (0.02-11.97)
Age	0.99 (0.97-1.01)	0.97 (0.95-1.00)	1.02 (0.99-1.05)	0.97 (0.96-1.01)	1.00 (0.98-1.02)	0.97 (0.95-1.01)	1.01 (0.97-1.05)	1.02 (0.98-1.06)
Tumor length	1.00 (0.91-1.10)	1.02 (0.89-1.18)	1.14 (0.88-1.49)	0.93 (0.78-1.12)	0.98 (0.87-1.11)	1.00 (0.85-1.19)	0.85 (0.57-1.27)	0.96 (0.74-1.26)
Location tumor								
- Mid esophagus	1	1	1	1	1	1	1	1
- Distal esophagus	1.05 (0.71-1.57)	1.28 (0.68-2.41)	1.18 (0.54-2.55)	0.82 (0.38-1.78)	0.96 (0.58-1.58)	1.35 (0.65-2.78)	0.64 (0.22-1.84)	0.60 (0.17-1.52)
- Gastric cardia	1.19 (0.69-2.05)	1.39 (0.53-3.66)	0.72 (0.27-1.95)	1.46 (0.57-3.84)	0.79 (0.37-1.70)	0.74 (0.23-2.97)	0.29 (0.06-1.37)	1.35 (0.34-5.43)
Prior radiation and/or chemotherapy								
- No	1	1	1	1	1	1	1	1
- Yes	1.34 (0.90-2.01)	1.01 (0.52-1.99)	2.25 (0.96-5.25)	1.52 (0.72-3.19)	1.30 (0.77-2.21)	1.11 (0.51-2.44)	0.73 (0.23-2.27)	2.76 (0.93-8.15)
Type of stent								
- Ultraflex stent	1				1			
- Gianturco Z-stent	1.62 (0.88-3.00)				1.12 (0.52-2.40)			
- Flamingo Wallstent	1.30 (0.82-2.04)				0.82 (0.45-1.48)			
Length of stent cover	0.97 (0.83-1.13)	0.88 (0.72-1.07)	0.89 (0.60-1.31)	2.62 (1.03-6.64)	0.99 (0.82-1.20)	0.90 (0.72-1.13)	1.33 (0.74-2.38)	1.38 (0.30-6.41)

(Table 4: continued)

	Minor complications				Recurrent dysphagia			
Characteristics	**Overall HR (95%CI)**	**Ultraflex stent HR (95%CI)**	**Gianturco Z-stent HR (95%CI)**	**Flamingo Wall stent HR (95%CI)**	**Overall HR (95%CI)**	**Ultraflex stent HR (95%CI)**	**Gianturco Z-stent HR (95%CI)**	**Flamingo Wall stent HR (95%CI)**
Diameter								
- Small	1	1	1	1	1	1	1	1
- Large	0.94 (0.47-1.88)	0.72 (0.19-2.74)	2.76 (0.68-11.26)	0.09 (0.01-0.74)	0.35 (0.17-0.73)	0.16 (0.04-0.74)	0.79 (0.11-8.67)	0.40 (0.03-4.79)
Age	0.98 (0.96-1.01)	0.97 (0.93-1.01)	1.03 (0.98-1.07)	0.97 (0.93-1.00)	0.99 (0.98-1.01)	0.99 (0.97-1.02)	1.03 (0.98-1.08)	0.97 (0.94-1.00)
Tumor length	1.05 (0.92-1.20)	1.16 (0.94-1.44)	1.35 (0.97-1.87)	0.89 (0.69-1.15)	1.01 (0.91-1.13)	1.11 (0.97-1.28)	1.17 (0.80-1.73)	0.86 (0.65-1.13)
Location tumor								
- Mid esophagus	1	1	1	1	1	1	1	1
- Distal esophagus	1.31 (0.74-2.32)	1.42 (0.48-4.19)	1.39 (0.53-3.62)	1.40 (0.50-3.95)	1.03 (0.67-1.56)	1.07 (0.59-1.94)	0.52 (0.19-1.45)	1.56 (0.65-3.79)
- Gastric cardia	1.86 (0.91-3.83)	3.02 (0.77-11.84)	0.66 (0.17-2.50)	2.06 (0.58-7.31)	1.10 (0.56-2.19)	1.19 (0.61-3.49)	0.38 (0.10-1.52)	3.01 (0.63-14.38)
Prior radiation and/or chemotherapy								
- No	1	1	1	1	1	1	1	1
- Yes	1.46 (0.83-2.55)	0.78 (0.27-2.22)	4.27 (1.44-12.71)	1.27 (0.47-3.46)	1.23 (0.79-1.92)	1.19 (0.61-2.33)	1.76 (0.62-4.99)	1.01 (0.43-2.36)
Type of stent								
- Ultraflex stent	1				1			
- Gianturco Z-stent	2.75 (1.11-6.84)				0.61 (0.31-1.22)			
- Flamingo Wallstent	1.77 (0.93-3.37)				1.03 (0.63-1.70)			
Length of stent cover	0.89 (0.71-1.11)	0.75 (0.54-1.06)	0.70 (0.43-1.15)	3.25 (1.08-9.80)	1.02 (0.87-1.20)	0.98 (0.81-1.19)	0.73 (0.43-1.25)	1.10 (0.32-3.78)

rhage, perforation, fistula formation, fever and pain (5). Recently, investigators from the UK described 3 patients who developed esophagorespiratory fistula at the proximal end of a large-diameter Flamingo Wallstent (8). In all cases, these fistulas became clinically relevant 7-11 months after placement. For that reason, they recommended not to use large-diameter stents in patients with a life expectancy longer than 6 months. In the present study, complications for the whole group of patients were not different from those found in other studies in which patients were followed prospectively (4-7). We found, however, more stent-related complications in patients treated with a large-diameter Gianturco Z-stent, compared in those treated with a large-diameter Ultraflex stent or Flamingo Wallstent (Table 3). In addition, minor complications, particularly pain, were more frequently seen in patients treated with a Gianturco-Z stent, irrespective of its size. Although not proven, it might well be that this is caused by the design of the Gianturco-Z stent. This stent consists of a wide "Z"-mesh of stainless steel and is considered to be the least flexible stent of all stents currently available (2). The metal barbs on the outside of the stent may additionally have caused damage to the esophageal wall. Remarkably, increasing the size of the stent or the length of the cover of the Flamingo Wallstent was found to protect against the development of minor complications. The mechanism of this protective effect remains, however, unclear.

Recurrent dysphagia caused by tissue overgrowth was seen in 47 patients with a small-diameter stent and, surprisingly, in only 5 patients treated with a large-diameter stent (Table 3). Tissue overgrowth may be caused by tumor tissue due to progressive tumor growth or by non-malignant hyperplastic tissue growth at the end of the stent. It has been demonstrated that tissue overgrowth from non-malignant obstructive tissue is more likely to occur in patients with a prolonged survival. Mayoral et al. (9) showed the presence of hyperplastic tissue overgrowth at the ends of covered stents in 32% of patients after a mean interval of 22 weeks. It can be speculated that large-diameter stents exert a greater force on the esophageal wall than small-diameter stents. This greater force could induce fibrosis and proliferation of granulation tissue at the end of the stent. In these cases, it has been demonstrated that the esophageal wall shows mucosal denudation, deep impaction of the stent mesh into the esophageal wall, and the development of new reactive strictures at both ends of the stent (10). Tissue overgrowth hardly occurred in patients treated with a large-diameter stent in the present study. In 32/52 (62%) patients with recurrent dysphagia, tissue overgrowth was observed at the proximal end of the stent. After stent placement in the mid or proximal esophagus, tissue overgrowth may occur at both the proximal and distal end of the stent, whereas, with stents placed across the GEJ (with the distal end of the stent not anchored in tissue), tissue overgrowth only can occur at the proximal end of the stent. Multivariable analysis showed, however, that the risk of recurrent dysphagia was not affected by tumor location (Table 4). Moreover, as median survival was relatively short and not statistically significant different between patients with a small- or a large-diameter stent (Table 2), it seems likely that nonmalignant tissue overgrowth did not play a predominant role in the recurrence of

dysphagia. Instead, recurrent dysphagia is likely caused by recurrent tumor growth. However, because the ratio between total length of the covered part of the stent and tumor length was also not different between the two treatment groups (Table 1), it remains to be established what the exact role of stent size is in the prevention of tumor overgrowth.

In conclusion, our results demonstrate that large-diameter stents reduce the risk of recurrent dysphagia due to stent migration, tissue overgrowth or food obstruction. Increasing the diameter in some stent types, however, may increase the risk of stent-related complications to the esophagus. We recognize, however, that our results are based on retrospective data. Therefore, further, preferably randomized, studies are needed to compare efficacy, risk of complications and recurrent dysphagia between small- and large-diameter stents, and among different stent designs.

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5D

Esophageal stents for malignant strictures close to the upper esophageal sphincter

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ABSTRACT

Background: Self-expanding stents are a well accepted palliative treatment modality for strictures due to esophageal carcinoma. However, the use of stents close to the upper esophageal sphincter is considered to be limited by patient intolerance caused by pain and globus sensation, and an increase risk of complications, particularly tracheoesophageal fistula formation and aspiration pneumonia.

Objectives: To determine the efficacy and safety of stent placement in patients with a malignant obstruction close to the upper esophageal sphincter (UES).

Design: Evaluation of 104 patients with dysphagia from a malignant stricture close the upper esophageal sphincter treated in the period 1996-2006.

Setting: Single university center.

Patients: Patients with primary esophageal carcinoma (n=66) or recurrent cancer after gastric tube interposition (n=38) within 8 cm distance distal of the UES. Twenty-four (23%) patients also had a tracheo-esophageal fistula.

Interventions: Stent placement.

Main outcome measurements: Functional and technical outcome, survival, complications and recurrent dysphagia. Analyses were performed by chi-square test, Kaplan-Meier curves and log rank testing.

Results: Mean distance from the UES to the upper tumor margin was 4.9 ± 2.6 cm, and to the upper stent margin was 3.1 ± 2.3 cm. The procedure was technically successful in 100/104 (96%) patients. Fistula sealing was achieved in 19/24 (79%) patients. After 4 weeks, dysphagia had improved from a median score of 3 (liquids only) to 1 (some difficulties with solids). Total complications were seen in 34/104 (33%) patients. Of these, major complications (aspiration pneumonia (9), hemorrhage (8), fistula (7) and perforation (2)) occurred in 22 (21%) patients, whereas pain following stent placement was observed in 16 (15%) patients. Recurrent dysphagia occurred in 29 (28%) patients and was mainly caused by tissue in- or overgrowth (n=10), food bolus obstruction (n=7), stent migration (n=3), or other reasons (n=11), such as persistent fistula (n=5), difficulty with swallowing (n=4), and dislocation of the stent (n=2). Eight (8%) patients complained of globus sensation, however, in none of the patients stent removal was indicated.

Limitations: Retrospective design.

Conclusions: Stent placement is safe and effective for the palliation of dysphagia and sealing of fistulas in patients with a malignant stricture close to the UES. Based on these results, stent placement may be considered for palliation in this group of patients with an otherwise dismal prognosis.

INTRODUCTION

Despite recent advances in the treatment of esophageal cancer (1), still 50-60% of patients present with incurable disease. For these patients, palliative therapy to relieve dysphagia is the only treatment option available. Self-expanding stents are a well accepted treatment modality for malignant esophageal disease.

Tumors close to the upper esophageal sphincter (UES) (7-10% of all esophageal carcinomas) are traditionally regarded as more difficult to manage, as stents in the proximal esophagus are considered to be associated with an increased risk of complications, such as perforation, aspiration pneumonia, proximal migration, and patient intolerance caused by pain and globus sensation (2, 3), and hence radiation therapy is often the treatment of choice. Recently, this view has begun to evolve, as some small studies have reported successful insertion of stents at this location (4-8). The results in these studies suggest that malignant strictures and/or fistulas in the proximity of the UES should no longer be considered a contraindication for palliative stent placement.

In the current study, we determined efficacy and safety of stent placement in a cohort of patients with a malignant obstruction close to the UES as a result of a primary esophageal carcinoma or recurrent cancer after previous gastric tube interposition.

PATIENTS AND METHODS

Patients

From January 1996 to June 2006, 648 patients were treated with a stent in the esophagus or gastric cardia at the Erasmus MC Rotterdam. Data from these patients are collected in a prospective database. Informed consent of patients to analyze this information is not needed in The Netherlands. From this database, we included patients with an inoperable malignant obstruction of the esophagus within 8 cm of the UES. A tumor was considered inoperable if the patient had distant metastases, local tumor infiltration in neighboring organs, and/or a poor health due to concomitant disease. Exclusion criteria were recurrent tumor after gastrectomy, previous stent placement, obstruction due to extrinsic compression, and benign strictures. Patients with an incomplete follow-up and patients who were unfit to undergo conscious sedation were also excluded. In total, 104 patients fulfilled the in- and exclusion criteria.

All patients were evaluated before stent placement and at approximately 4-weeks intervals after stent placement until death. Evaluations were performed by telephone calls to the patient and the general practitioner, and included the following items: 1) ability to eat and/or swallow (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 grade 4: complete

dysphagia) (9); and 2) specific symptoms such as pain, heartburn, regurgitation, and weight loss. In case of complications or recurrent dysphagia, patients were seen for evaluation and treatment. If a patient was referred to another center for a complication or recurrent dysphagia, the relevant clinical information was obtained from that hospital.

Placement of stents

Prior to stent placement, a CT-scan of the thorax was made in all patients, with an additional bronchoscopy in case tumor infiltration in or extrinsic compression on the trachea was suspected. During stent insertion, all patients were consciously sedated with midazolam (Dormicum®, Roche Nederland BV, Mijdrecht, the Netherlands). If it was impossible to pass the tumor with an endoscope, the stricture was dilated to a maximum of 10 mm by a Savary-Miller Esophageal Dilator (Wilson-Cook Medical, Winston-Salem, NC). The upper and lower tumor margins were, if possible, marked with sclerotherapy needle-injected radiographic contrast material or, alternatively, with a radiopaque marker placed on the skin. The stents were advanced over a guidewire into the esophagus. The stents were mostly deployed under fluoroscopic monitoring, however, in some instances the stent was deployed under endoscopic view with the UES used as landmark. A stent of 2-4 cm longer than the stricture was chosen to allow for at least a 1 cm, but preferably a 2 cm extension above and below the proximal and distal tumor shoulder. After stent placement, the position was endoscopically controlled under direct vision. In some cases, X-ray imaging and a barium-swallow were additionally performed.

Statistical analysis

The following clinical characteristics were considered: age, gender, dysphagia score before stent placement, tumor length, distance between UES and tumor, distance between UES and upper margin of stent, histology, dilation before stent placement, type of stent, prior radiation and/or chemotherapy, and presence of an esophagorespiratory fistula. Outcome included technical success of stent placement, dysphagia score after stent placement, complications, recurrent dysphagia, 30-day mortality and survival.

The results were expressed as means ± standard deviation (SD), and as medians with interquartile range (IQR) as required. Long term survival was expressed as median survival. Dysphagia scores at 4 weeks after stent placement were analyzed using covariance analysis with dysphagia score before treatment taken as covariate. Complications and treatment for 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. Factors influencing occurrence of complications and recurrent dysphagia were analyzed using Cox regression analysis with type of tumor (primary or recurrent), age, gender, tumor length, location of the stricture (≤ 4 cm or 5-8 cm of UES), distance between UES and upper margin of the stent, type of stent, and prior radiation and/or chemotherapy as covariates. A p-value

<0.05 was considered statistically significant. All analyses were conducted using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

Clinical characteristics of the 104 patients with a malignant stricture close to the UES treated with a stent and fulfilling the inclusion criteria are shown in Table 1. Twenty four (23%) patients also had an esophagorespiratory fistula. Four (4%) patients received a stent in both the trachea and esophagus. In these patients, the tumor had infiltrated into the trachea or gave extensive extrinsic compression on the trachea. In order to prevent airway compression following esophageal stent placement, initially a trachea stent was inserted. Patients were treated with different types of stents, with a preference in 50/104 (48%) patients for an Ultraflex stent (Boston Scientific, Natick, USA), particularly in those with a tumor within 4 cm of the UES (Figure 1). Large diameter stent were more frequently used in patients with recurrent cancer following esophagectomy (p=0.008). The patients with a stricture within 4 cm of the UES and treated with a large diameter stent all had recurrent tumor. Mean distance between the UES and the tumor was 4.9 ± 2.6 cm, whereas mean distance between the UES and the upper margin of the stent was 3.1 ± 2.3 cm. In 44/104 (42%) patients, the stricture was located within 4 cm of the UES. Mean tumor length was 7.0 cm, however, tumor length was longer in patients with primary esophageal carcinoma compared to those with recurrent cancer after esophagectomy with gastric pull-up (7.8 vs. 5.5 cm; p=0.002). Forty five (43%) patients underwent prior radiation and/or chemotherapy. Patients with a stricture within 4 cm of the UES more often had undergone prior radiation and/or chemotherapy compared to those with a stricture within 5-8 cm of the UES (25/44 (57%) vs. 21/60 (35%); p=0.03) (Table 1).

Outcome and survival

The procedure was technically successful in 100/104 (96%) patients (Table 2). Causes of technical failure included stent migration during placement (n=2) with the stent being repositioned in both patients, inadequate stent length in one patient for which a second stent was successfully inserted, and compression on the trachea in one patient. In this patient no stent was inserted, but instead a nasoduodenal feeding tube was placed. The esophagorespiratory fistula was sealed in 19/24 (79%) patients. Of these, five patients had recurrent leakage after 7, 7, 12, 21 and 35 days, respectively. Four of these patients were successfully treated with a second stent. A fifth patient with recurrent leakage underwent conservative treatment, which included antibiotics, nil per mouth and feeding through a nasoduodenal

Table 1. Clinical characteristics of 104 patients with a malignant stricture close to the upper esophageal sphincter (UES)

	All patients n=104	Primary esophageal carcinoma n=66	Recurrent cancer after esophagectomy n=38	p-value	Stricture ≤ 4cm of UES n=44	Stricture 5-8 cm of UES n=60	p-value
Age (y); mean ± sd	66 ± 11	67 ± 12	64 ± 9	0.27	66 ± 11	65 ± 12	0.67
Male; no. of patients (%)	72 (69)	43 (65)	29 (76)	0.24	31 (70)	41 (68)	0.82
Dysphagia score before treatment; median (IQR*)	3 (1)	3 (1)	4 (1)	0.67	4 (1)	3 (1)	0.56
Tumor length, cm; mean ± sd	7.0 ± 3.2	7.8 ± 3.0	5.5 ± 3.0	<0.001	6.3 ± 2.7	7.5 ± 3.5	0.06
Distance between UES and tumor; cm; mean ± sd	4.9 ± 2.6	5.2 ± 2.6	4.5 ± 2.6	0.21	2.6 ± 1.5	6.7 ± 1.7	<0.001
Distance between UES and upper margin of stent; cm; mean ± sd	3.1 ± 2.3	3.4 ± 2.4	2.6 ± 2.0	0.07	1.2 ± 1.3	4.5 ± 1.8	<0.001
Prior esophagorespiratory fistula; no. of patients (%)	24 (23)	13 (20)	11 (32)	0.28	7 (16)	17 (15)	0.14
Histology; no. of patients (%)				<0.001			0.57
Squamous cel carcinoma	67 (64)	55 (83)	12 (32)		27 (61)	40 (67)	
Adenocarcinoma	32 (32)	9 (14)	24 (63)		16 (36)	17 (28)	
Unknown	4 (4)	2 (3)	2 (5)		1 (3)	3 (5)	
Prior radiation and/or chemotherapy; no. of patients (%)							
Total	45 (43)	31 (47)	14 (37)	0.46	25 (57)	21 (35)	0.03
Chemotherapy	18	10	8		5	13	
Radiation	9	7	2		6	3	
Radiation and chemotherapy	18	14	4		13	5	
Size of stent; no. of patients (%)				0.008			0.12
Small	85 (82)	59 (89)	26 (68)		39 (89)	46 (77)	
Large	19 (18)	7 (11)	12 (32)		5 (11)	14 (23)	
Type of stent; no. of patients (%)				0.98			0.05
Ultraflex stent	50 (48)	32 (48)	18 (47)		25 (57)	25 (42)	
Gianturco- Z stent	28 (27)	17 (26)	11 (29)		14 (32)	14 (23)	
Flamingo Wallstent	15 (14)	10 (15)	5 (13)		2 (5)	13 (22)	
Other	11 (11)	7 (11)	4 (11)		3 (6)	8 (13)	

* IQR = interquartile range

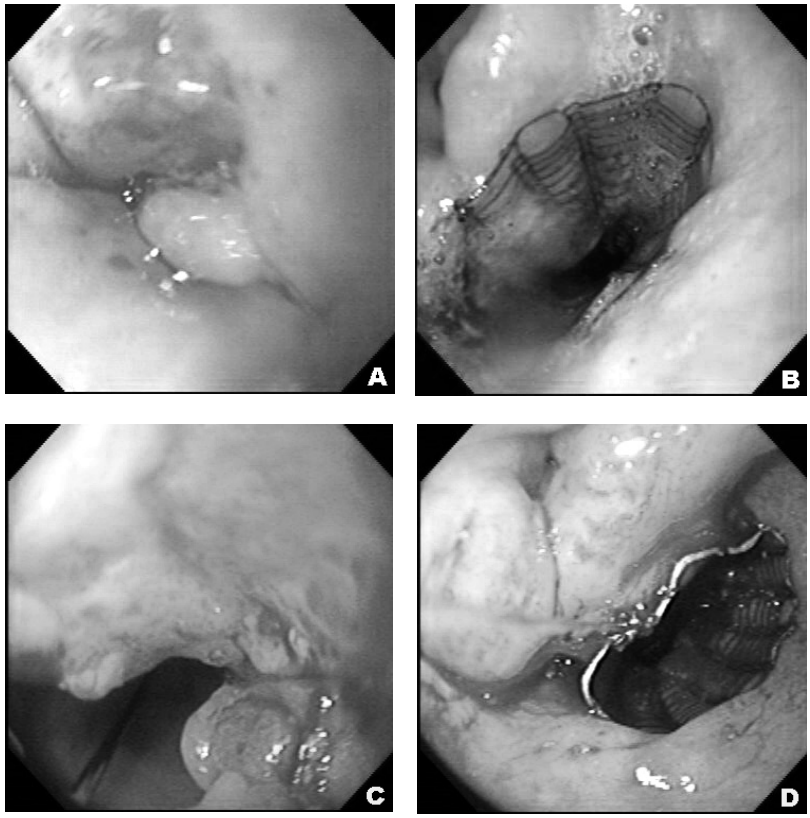

Figure 1. (a) Primary esophageal cancer 2 cm below the upper esophageal sphincter (UES). This patient was inoperable because of metastases and a poor medical condition. (b) An Ultraflex stent was inserted. Note the position of the stent in relation to the UES directly after placement. The stent usually slightly shortens over the subsequent 6-12 hours which causes the stent to be positioned in a good final position. (c) Recurrent cancer 2-3 cm below the UES in the esophageal remnant 14 months after partial esophageal resection with gastric pull-up. Note the guidewire in the esophageal lumen. (d) An Ultraflex stent was placed which was finally positioned just below the UES.

tube. Nevertheless, this patient died from progressive respiratory failure as a consequence of aspiration pneumonia.

The dysphagia score improved from a median of 3 (liquids) to 1 (some difficulties with solids) ($p<0.001$). The degree of improvement was not different between patients with primary esophageal carcinoma or recurrent cancer after esophagectomy ($p=0.67$), or between patients with a stricture within 4 cm or 5-8 cm of the UES ($p=0.61$) (Table 2). Globus sensation was seen in 8 (8%) patients with a stricture within 4 cm of the UES, however, in none of the patients stent removal was indicated. Median survival was 95 (primary tumor) and 66 (recurrent tumor) days ($p=0.14$), and 75 (≤ 4 cm of UES) and 115 (5-8 cm of UES) days, respectively ($p=0.01$). The vast majority of patients (77/99 (78%)) died from tumor progression. Nine of 66 (14%) patients with primary cancer died within 30 days, compared to 12/38 (35%) patients

Table 2. Outcome and survival in 104 patients with a malignant stricture close to the upper esophageal sphincter (UES)

	All patients n=104	**Primary esophageal carcinoma n=66**	**Recurrent cancer after esophagectomy n=38**	**p-value**	**Stricture ≤ 4cm of UES n=44**	**Stricture 5-8 cm of UES n=60**	**p-value**
Technical success; no. of patients (%)	100 (96)	64 (97)	36 (95)	0.57	42 (95)	58 (97)	0.75
Dilation before treatment; no. of patients (%)	31 (30)	19 (29)	12 (32)	0.76	17 (39)	14 (23)	0.09
Dysphagia score 4 wks after treatment; median (IQR*)	1 (1)	1 (1)	1 (1)	0.67	1 (1)	1 (1)	0.61
30-day mortality; no. of patients (%)	21 (21)	9 (14)	12 (35)	0.04	8 (18)	13 (22)	0.63
Median survival in days	79	95	66	0.14	75	115	0.01
Cause of death; no. of patients (%)				0.62			0.71
Stent-related	7 (7)	3 (5)	4 (12)		3 (6)	4 (7)	
Tumor progression	77 (78)	51 (78)	26 (76)		35 (79)	44 (73)	
Unknown	14 (14)	10 (15)	4 (12)		7 (15)	12 (20)	

* IQR = interquartile range

with recurrent tumor (p=0.04). Thirty-day mortality was not different between patients with a stricture within 4 cm or 5-8 cm of the UES (8 (18%) vs. 13 (22%); p=0.63) (Table 2).

Complications and recurrent dysphagia

Complications were observed in 34/104 (33%) patients (Table 3). Major complications (aspiration pneumonia (9), hemorrhage (8), fistula (7) and perforation (2)) occurred in 22 (21%) patients and were not different between patients with a primary tumor or recurrent tumor (13 (20%) vs. 9 (24%); p=0.26), or between patients with a stricture within 4 cm or 5-8 cm of the UES (8 (18%) vs. 14 (23%); p=0.85). Aspiration pneumonia occurred in nine (9%) patients. Five patients were successfully treated with antibiotics. Four patients died from progressive respiratory failure as a consequence of pneumonia. Hemorrhage was observed in 8 (8%) patients. Three patients with hemorrhage were successfully treated with additional radiation therapy, whereas three other patients required at least one blood transfusion. Two patients died as a consequence of hemorrhage. As these patients were already in a poor medical condition due to progressive metastatic disease when hemorrhage occurred, no diagnostic procedures were performed. Seven (7%) patients developed an esophagorespiratory fistula during follow-up. In six patients, the fistula was successfully sealed by a second stent. One patient with persistent leakage alongside the stent died from septic complications. Perforation occurred in two (2%) patients. In one patient, the perforation was observed after dilation that preceded stent placement. This perforation was sealed by the inserted stent. In another patient, a small perforation was observed at the proximal end of the inserted stent. This patient was treated conservatively with antibiotics, nil per mouth and feeding through a nasoduodenal tube. After seven days, a swallow X-ray with gastrografin (Schering Netherlands BV, Weesp, the Netherlands) showed no evidence of perforation. The patient gradually resumed eating, and within one week he was able to eat an almost normal diet.

Minor complications, mainly retrosternal pain, were seen in 14 patients with a primary tumor and in two patients with recurrent tumor (Table 3). There was no difference in occurrence of minor complications between patients with a stricture within 4 cm of the UES compared to those with a stricture within 5-8 cm of the UES (8 (18%) vs. 8 (13%); p=0.48). The pain was clearly related to stent placement in all patients. In nine patients, pain following stent placement required treatment with analgesics for at least one week.

Recurrent dysphagia occurred in 29 (28%) patients and was caused by tissue in- or overgrowth (n=10), food bolus obstruction (n=7), stent migration (n=3), or other reasons (n=11), such as persistent fistula (n=5), difficulty with swallowing (n=4), and partial collapse of the upper rim of the stent (n=2) (Table 3). Tissue in- or overgrowth, stent migration or a persistent fistula was, depending on the clinical condition and prognosis of the patient, treated with insertion of a second stent. In the patients with difficulty in swallowing, endoscopy showed an open stent, whereas barium swallow revealed good passage through the stent. Nevertheless, these patients received a nasoduodenal tube for feeding. Tissue in- or overgrowth occurred

Table 3. Complications and recurrent dysphagia in 104 patients with a malignant stricture close to the upper esophageal sphincter (UES)

	All patients n=104 no. of patients (%)	**Primary esophageal carcinoma n=66 no. of patients (%)**	**Recurrent cancer after esophagectomy n=38 no. of patients (%)**	**p-value***	**Stricture ≤ 4cm of UES n=44 no. of patients (%)**	**Stricture 5-8 cm of UES n=60 no. of patients (%)**	**p-value***
Total complications	44 in 34 pts (33)	30 in 23 pts (35)	14 in 11 pts (29)	0.94	16 in 13 pts (30)	28 in 21 pts (35)	0.86
Major complications	27 in 22 pts (21)	15 in 13 pts (20)	12 in 9 pts (24)	0.26	8 in 8 pts (18)	19 in 14 pts (23)	0.85
- (aspiration) pneumonia	9	3	6		2	7	
- hemorrhage	8	6	2		1	7	
- fistula	7	5	2		3	4	
- perforation	2	1	1		2	-	
- other	1	-	1		-	1	
Minor complications	17 in 16 pts (15)	15 in 14 pts (21)	2 in 2 pts (5)	0.05	8 in 8 pts (18)	9 in 8 pts (13)	0.48
- pain	16	14	2		8	8	
- gastro-esophageal reflux	1	1	-		-	1	
Recurrent dysphagia	27 in 29 pts (28)	16 in 15 pts (23)	15 in 14 pts (37)	0.01	12 in 12 pts (27)	19 in 17 pts (28)	0.13
- tissue growth	10	4	6		2	8	
- food bolus obstruction	7	6	1		1	6	
- migration	3	2	1		1	2	
- other	11	4	7		8	3	

* Log rank test for time to first complication

after 16, 20, 41 and 46 weeks in patients with primary esophageal carcinoma, and after 2 (n=2), 17 (n=2), 67 and 112 weeks in patients with recurrent cancer after esophagectomy.

Factors influencing occurrence of complications and recurrent dysphagia

Multivariable analysis showed that the occurrence of major complications was not influenced by type of tumor (primary or recurrent tumor), age, gender, tumor length, distance between UES and tumor, distance between UES and upper margin of the stent, stent type, or prior radiation and/or chemotherapy (Table 4). Pain after stent placement was associated with type of tumor (primary tumor vs. recurrent tumor: 14/66 (21%) vs. 2/38 (5%); HR: 5.88; 95%CI 1.14-30.30) (Table 4). Recurrent dysphagia was associated with gender (male vs. female: 7/72 (10%) vs. 9/32 (28%); HR: 0.26; 95%CI 0.09-0.82) and with type of stent. Particularly, Gianturco-Z stents (HR: 4.61; 95%CI 1.52-14.02) and Flamingo Wallstents (HR: 6.45; 95%CI 1.81-23.05) were associated with an increased risk of recurrent dysphagia (Table 4).

DISCUSSION

Self-expanding stent placement is nowadays an accepted treatment modality for patients with irresectable primary carcinoma of the mid and distal esophagus and gastric cardia (10-13). However, the efficacy and safety of stents for the palliation of dysphagia in patients with malignant strictures, either primary (4-8) or following esophagectomy (14-16), in the proximal esophagus close to the UES is less well documented.

The current study shows that metal stents can well be used to bridge malignant strictures and seal malignant fistulas in the proximal esophagus. This will likely increase the quality of life in this group of patients with a dismal prognosis. Moreover, apart from pain after stent placement, which was more frequently seen in patients with primary esophageal cancer, no differences in complications were found between stents placed for primary malignancies or recurrent tumor around the anastomotic site following esophagectomy with gastric tube reconstruction. In addition, no differences were found in occurrence of complications and recurrent dysphagia between patients with a stricture within 4 cm or 5-8 cm of the UES. Finally, recurrent dysphagia after stent placement was least likely with Ultraflex stents in the proximal esophagus, suggesting that stent design is an important factor in determining an optimal palliative result after stent placement.

During stent deployment in the proximal esophagus it is obvious that endoscopic visualization and/or fluoroscopic monitoring are important to control precise position of the proximal end of the stent just below the UES. In this study, stent placement was technically successful in 96% patients (Table 2). In only two patients, the stent migrated during placement. This could be corrected by repositioning the stent. The dysphagia score improved from a median of 3 (liquids) to 1 (some difficulties with solids) ($p<0.001$). The dysphagia score did

Table 4. Factors influencing the occurrence of major complications, pain and recurrent dysphagia in 104 patients with a malignant stricture close to the upper esophageal sphincter (UES)

	Major complications		Pain		Recurrent dysphagia	
Characteristics	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Type of tumor						
- recurrent tumor	1	-	1	-	1	-
- primary tumor	0.64	0.23-1.78	5.88 [a]	1.14-30.30	0.37	0.14-1.02
Age	0.98	0.94-1.02	1.01	0.96-1.07	0.99	0.95-1.04
Gender						
- male	1	-	1	-	1	-
- female	1.77	0.71-4.44	2.66	0.90-7.85	0.26 [b]	0.09-0.82
Tumor length	1.00	0.86-1.18	0.84	0.66-1.06	0.95	0.80-1.12
Location stricture						
- ≤ 4 cm of UES	1	-	1	-	1	-
- 5-8 cm of UES	0.75	0.16-3.55	1.58	0.27-9.43	0.61	0.19-1.98
Distance between UES and upper margin of stent	1.03	0.73-1.44	0.86	0.61-1.28	0.78	0.60-1.03
Type of stent						
- Ultraflex stent	1	-	1	-	1	-
- Gianturco-Z stent	0.87	0.29-2.60	1.15	0.31-4.35	4.61 [c]	1.52-14.02
- Flamingo Wall stent	1.44	0.42-4.91	1.28	0.27-6.07	6.45 [d]	1.81-23.05
- other	0.45	0.06-3.69	1.07	0.18-6.75	2.87	0.65-12.66
Chemotherapy and/or radiation						
- no	1	-	1	-	1	-
- yes	0.94	0.36-2.47	1.93	0.58-6.46	1.09	0.43-2.75

[a] p=0.03
[b] p=0.02
[c] p=0.007
[d] p=0.004

not improve in patients who had difficulty with swallowing and with unsuccessfully sealed fistulas. Covered stents have been reported to be successful in sealing esophagorespiratory fistulas in 70-100% of patients (14, 17-23). This is in accordance with findings in the present series with a success rate of 79% in sealing tracheoesophageal fistulas. One should, however, realize that the reported results, so far, (14, 17-23) were largely based on fistulas in the mid or distal part of the esophagus, in which position stent placement is probably less demanding compared to the proximal esophagus.

The use of stents in the proximal esophagus has traditionally been considered to be limited because of an increased risk of complications and patient intolerance. Our results showed that a malignant stricture in the proximity of the UES should no longer be considered as a contraindication for the use of stents. In total, complications were observed in 34 of 104 (33%) patients (Table 3). This incidence is in accordance with that found in other, but smaller series of stents placed for complicated (fistulas, proximal esophagus) or recurrent cancer after esophagectomy (4, 20, 24, 25). In addition, compared with series of stents placed in the mid- or distal esophagus or gastric cardia, the complication rate is also comparable, with reported frequencies varying between 24-36% (11, 12, 26-28). In contrast, Wang et al. (23) evaluated delayed complications in 82 patients with malignant esophageal strictures or esophagorespiratory fistulas. The overall incidence of delayed complications was 65%, with 21% of patients experiencing more than one complication. Complications occurred more frequently when stents were placed in the proximal third of the esophagus (23). It might well be that this difference in outcome can be explained by differences in survival between patients in our series (median survival: 79 days) and those in the study of Wang et al. (mean survival: 4.5 months), suggesting that with longer survival the risk of complications increases. Pain following stent placement occurred in 16 (15%) patients and was associated with type of tumor, with more patients experiencing pain in case of a primary esophageal carcinoma (Table 4). Although some studies have suggested that an increased risk of complications, particularly pain, is associated with previous radiation and/or chemotherapy (29), this could not be confirmed in the present study (Table 4), nor in other series (11, 30, 31).

In order to minimize patient intolerance, complications and recurrent dysphagia, and to increasing sealing rates if a fistula is present, stent design is an important consideration. What is the ideal design if the stent is placed in the proximal esophagus close to the UES? In our opinion, the ideal stent should not shorten and be flexible to optimally adjust to the luminal configuration. In addition, it needs to have a moderate expansive force and a maximum body diameter of 18 mm to avoid globus sensation and tracheal compression. Finally, it should deploy from proximal to distal to optimize placement close to the UES, and be covered to prevent tumor ingrowth and to seal any coexisting fistula. For patients with recurrent cancer after esophagectomy, the optimal stent diameter sometimes needs to be larger to effectively cover the dilated lumen of the gastric tube interposition. In our experience, the Ultraflex stent (Boston Scientific, Natick, USA), with its relatively low radial force and less rigidity compared to other stent designs, may presently be preferable in patients with malignant strictures in the proximal esophagus. Multivariable analysis showed that the occurrence of major complications or pain was not affected by stent type (Table 4). Recurrent dysphagia, however, was more frequently observed in patients treated with a Gianturco-Z stent or Flamingo Wallstent. These results support the use of Ultraflex stents in patients with malignant strictures close to the UES. Recently, South Korean investigators have reported their experience in three patients with malignant strictures in the proximal esophagus who were treated with a newly

designed covered stent, characterized by a shorter length, 7 mm, of the upper flange (M.I. Tech Co., Ltd., Pyongteak, South Korea) (32). This stent was specifically designed to reduce foreign body sensation. In all three patients, the stent was successfully inserted, with a rapid improvement of dysphagia and no complications or foreign body sensation.

In conclusion, our results demonstrate that stent placement is safe and effective for the palliation of dysphagia and sealing of fistulas in patients with a malignant stricture close to the UES. We like to emphasize that physician experience with stent placement is important and is likely to influence patient outcome in this particularly challenging group of patients where precision in stent deployment is at a premium. We recognize that our results are based on retrospective data. Therefore, further prospective studies are needed to determine efficacy, risk of complications and recurrent dysphagia in patients with a complicated malignant stricture close to the UES.

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6

General discussion

NURSE-LED CARE FOR ESOPHAGEAL CANCER PATIENTS

In this thesis, we report the results of a randomized study comparing home visits by a specialist nurse with routine control visits to the outpatient clinic after surgery for esophageal cancer. Our aim was to compare these two follow-up strategies with regard to quality of life, medical outcome, patient satisfaction and costs. We concluded that follow-up of patients after curative esophageal cancer surgery could safely be performed by a specialist nurse at home. In addition, no differences in quality of life and satisfaction with care were found between patients in the nurse-led follow-up group and those followed at the outpatient clinic by physicians. Moreover, follow-up of these patients could result in a net cost reduction. Nurse-led follow-up may therefore be an alternative to regular control visits to the clinic for patients who have undergone treatment for esophageal cancer.

Prior to our randomized trial, we investigated the currently used follow-up strategies after surgery for gastrointestinal cancer in the Netherlands. We also reviewed published studies on tasks and procedures performed by nurses which are generally performed by physicians. Finally, we investigated which problems patients experience after resection for esophageal cancer and what care they expect from medical professionals. We speculated that the results of these studies could help in developing a patient-tailored strategy and involvement of nurses in counseling and treating patients with a malignant or chronic disorder of the gastrointestinal (GI) tract.

Perspectives and future research of nurse-led care

Nurses already increasingly perform tasks, such as the management and follow-up of patients with gastrointestinal disorders, and procedures, particularly endoscopic diagnostic procedures, which were usually performed by physicians. Studies have demonstrated that this is done in an efficient and safe way. For example, nurses adequately managed the follow-up of patients with Barrett's esophagus and inflammatory bowel disease. It is conceivable that nurses could also be involved in the management of patients with other chronic disorders of the GI tract, such as chronic pancreatitis and irritable bowel syndrome.

The demand for diagnostic and therapeutic endoscopy of the GI tract is rapidly increasing. This is caused by various factors, such as the introduction of new techniques and the increased awareness of screening and surveillance of premalignant disorders in the GI tract, such as Barrett's esophagus and adenomatous polyps of the colon. Nurses could well play an important role in performing diagnostic endoscopy. We recommend, however, performing of further studies before a widespread implementation is started in the Netherlands. A randomized study, comparing performance, patient experiences and costs of lower GI endoscopy between nurse and physician endoscopists, is currently being performed in the Netherlands.

Results from our randomized study have shown that specialist nurses were able to provide follow-up for patients after curative esophageal cancer surgery. As costs were lower in the nurse-led follow-up group, it is imaginable that nurse-led follow-up of patients with cancer in the GI tract could also be applied to patient groups with other types of cancer. Examples of these include malignancies in which recurrent or metastastic cancer means that no curative treatment options are available, for example pancreatic cancer and gastric cancer. Currently, we are performing a randomized trial evaluating the efficacy of nurses' involvement during follow-up of patients at a palliative stage of esophageal, pancreatic and hepatocellular cancer. Quality of life, medical effects, satisfaction and costs are the main outcome measures of this study.

ENDOSCOPIC PALLIATION OF DYPHAGIA FROM ESOPHAGEAL CARCINOMA

More than 50% of patients with esophageal cancer have inoperable disease at presentation. These patients are frequently treated with a self-expanding stent. In a randomized study, we compared three different stent types (Ultraflex stent, Poyflex stent and Niti-S stent) in patients with irresectable esophageal or gastric cardia cancer. The Ultraflex stent as well as the two new stent designs, i.e., the Polyflex stents and Niti-S stent, were safe and offered the same degree of palliation from malignant dysphagia. The newer stents had, however, the advantage that re-interventions were less frequently needed, as the Polyflex stent particularly reduced tissue overgrowth and the Niti-S stent migration rates.

Perspectives and future research of endoscopic palliation of dysphagia

A remaining drawback of stents in the esophagus is the occurrence of recurrent dysphagia caused by stent migration, tissue in- or overgrowth or food obstruction. We found that larger diameter stents were able to reduce the risk of recurrent dysphagia. Increasing the diameter of some stent types, particularly the Z stent, might, however, increase the risk of stent-related complications to the esophagus. Another option that was introduced was the addition of a wire mesh to the outer part of a fully-covered stent, the Niti-S stent. We showed that this stent design reduced recurrent dysphagia without jeopardizing safety of stent placement. If recurrent dysphagia can be reduced, this will also result in a reduction of re-interventions, which is cost-effective and may improve quality of life of patients.

It is important to stress that it is unlikely that the newer stent designs will be able to reduce the occurrence of complications, such as fistula formation and hemorrhage. The main reason for this is the fact that stent placement is a palliative procedure whereas at the same time the tumor is progressive and enlarging in size in all patients. We foresee that in the future combined modality treatments, for example radiation therapy and/or chemotherapy combined

with stent placement, will be able to reduce the occurrence of complications. In addition, these combined treatments could a prolong survival in (subgroups of) patients. Further studies are however needed to determine whether these policies are able to do so.

We found that stents efficiently improved dysphagia in patients with a malignant obstruction close to the upper esophageal sphincter. The risk of recurrent dysphagia after stent placement in the proximal esophagus was lowest with Ultraflex stents. This stent is already on the market for more than 10 years. The Ultraflex stent is a partially-covered and a highly flexible stent design with a relatively low expansion force as compared to other currently available stents. This study again showed that stent design is an important factor in determining an optimal palliative result after stent placement. In total, 8 (8%) patients complained of globus sensation after stent placement, however, in none of these patients stent removal was indicated. Recently, a new South Korean stent design was introduced for the palliation of malignant dysphagia in the proximal esophagus. This stent is characterized by a shorter length of the upper flange, which should reduce the risk of globus sensation (1). The stent was successfully inserted in three patients, with a rapid improvement of dysphagia and no complications or foreign body sensation. The next step is to compare this new stent design with the Ultraflex stent, preferable in a future randomized study.

It is clear that there is not a single stent that fits all patients with malignant dysphagia. Depending on the location (proximal vs. more distal), length and characteristics (extrinsic vs. exophytic; benign vs. malignant) of the tumor, a different stent design or even an alternative treatment should be chosen to adequately treat symptoms in a specific patient.

As has been demonstrated previously, stent placement is primarily reserved for patients with dysphagia and a short life expectancy (≤ 3 months), needing a rapid relief, but also for patients with persistent or recurrent tumor after single dose brachytherapy (2, 3). The aim is to improve food intake, which is associated with a positive effect on experienced quality of life of patients (4). Undernutrition is found in approximately 80% of patients presenting with dysphagia caused by esophageal cancer (5) and has not only a negative impact on quality of life of patients (6), but possibly also on post-operative complications (7) and survival of patients who undergo aggressive anticancer treatment (8, 9). It is therefore imaginable that stents could also be used as a bridge to curative treatment modalities for esophageal cancer, such as surgical resection (patients on a waiting list) with or without neo-adjuvant chemoradiation therapy, to prevent further deterioration of the nutritional condition of patients. It remains to be proven whether an improved nutritional condition as a consequence of stent placement, is indeed able to improve outcome in patients after curative treatment of esophageal cancer.

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Summary

Approximately 400,000 patients are annually diagnosed world-wide with esophageal cancer. If a patient is fit enough to undergo surgery and the tumor is considered resectable without evidence of distant metastases, a surgical resection is the primary treatment for esophageal cancer.

In order to investigate the currently used follow-up procedures after surgery for gastrointestinal cancer, we sent a questionnaire to all surgical departments in the Netherlands. The questionnaire focused on frequency of follow-up visits and diagnostic procedures after surgical treatment for esophageal, gastric, pancreatic and colorectal cancer. In the majority of hospitals, surgeons treated patients with colorectal and gastric cancer in their own centre, whereas patients with pancreatic and esophageal cancer were more often referred to a tertiary centre. After colorectal surgery, blood tests, colonoscopy and abdominal ultrasound were frequently performed. In other gastrointestinal malignancies, procedures were in most cases only performed if symptoms occurred. This survey indicated that at present follow-up after colorectal cancer surgery mainly focuses on finding recurrent disease and metachronous lesions in the colorectum, whereas this is less often the case after esophageal, gastric and pancreatic cancer surgery (**Chapter 2**).

Over the last 10 years, nurses increasingly perform tasks and procedures which were previously performed by physicians. We reviewed published studies regarding the types of gastrointestinal care and endoscopic procedures that nurses currently perform. In total, 19 studies were identified that evaluated performance of nurses in endoscopic practice. It was found that nurses accurately and safely performed upper endoscopy, endoscopic ultrasound, flexible sigmoidoscopy, video capsule endoscopy end percutaneous endoscopic gastrostomy placement. Two other studies demonstrated that nurses adequately managed follow-up of patients with Barrett's esophagus and inflammatory bowel disease. Four studies showed that patients were satisfied with the type of care nurses provided. Finally, it was suggested that costs were reduced if nurses performed sigmoidoscopy and evaluated capsule endoscopy examinations compared to physicians performing these activities. The findings of this review support the involvement of nurses in diagnostic endoscopy and follow-up of patients with chronic gastrointestinal disorders (**Chapter 3**).

We investigated which problems patients experience after a resection for esophageal cancer and what care they expect, in order to devise a better tailored follow-up policy. Therefore, we asked thirty patients, all within one year after esophageal cancer surgery, to fill out a questionnaire on experienced physical, psychological and social problems and on expected care for these problems. Additionally, a semi-structured interview was performed. The majority of patients experienced physical problems, such as a different eating pattern and fatigue, as problematic after esophagectomy. In addition, patients often felt depressed, were afraid

of metastases and death. Patients particularly expected professional care for physical issues related to their disease, whereas they often managed psychosocial problems in their own social network. Patients indicated that nurses' involvement during follow-up might improve their possibility to satisfactorily deal with problems (**Chapter 4A**).

In **Chapter 4B**, we compared routine control visits to the outpatient clinic with home visits by a specialist nurse with regard to quality of life, patient satisfaction and cost-effectiveness of follow-up of patients after intentionally curative surgery for esophageal cancer. Between January 2004 and February 2006, 109 patients were randomized to follow-up by surgeons at the outpatient clinic (usual follow-up) or by regular home visits of a specialist nurse (nurse-led follow-up) at 6 weeks and 3, 6, 9 and 12 months after randomization. We compared the two types of follow-up with respect to health-related quality of life (HRQoL), patient satisfaction, medical outcome and costs. Participating centers included one university and one general hospital in the Netherlands. Longitudinal data on disease specific and generic health-related quality of life (HRQoL) were collected at baseline at 6 weeks postoperatively and at 4, 7 and 13 months afterwards. Disease specific quality of life was assessed with the esophageal cancer specific EORTC QLQ-OES18 measure. Generic HRQoL was assessed using the oncology-specific EORTC QLQ-C30 measure, the EQ-5D including an index score and a visual analogue scale (EQ-VAS) for self-rated health, and the Hospital Anxiety and Depression scale (HAD). Patient satisfaction was assessed at seven months after randomization. A significant and clinically relevant improvement during follow-up in the eating scale (EORTC QLQ-OES18), the fatigue, physical, role and social functioning scales and global health (EORTC QLQ-C30), and the EQ-5D were found during follow-up, whereas other scales, for example the deglutition scale (EORTC QLQ-OES18) remained almost stable during follow-up. Scores on the HAD scale indicated that the patients were neither anxious nor depressed. We found no significant differences in HRQoL scores between the two follow-up groups over time. Although no differences were found in patient satisfaction between the follow-up groups, spouses in the nurse-led follow-up group were more satisfied with this novel type of care. In total, 11 (20%) patients in the nurse-led follow-up group and 16 (29%) patients undergoing usual care developed metastases at a median of 8 months after randomization. Of these patients, 14 (13%) patients died within one year after surgery.

Costs of medical services and, if necessary, palliative treatment were assessed during the follow-up visits. Costs of nurse-led follow-up visits were significantly lower than costs of usual follow-up visits (€232 vs. €453). Costs for intramural care were by far the highest cost category for both types of follow-up. Mean hospital stay was 8.9 days for nurse-led follow-up versus 17.8 days for usual follow-up. Costs for diagnostic procedures, additional treatments and extramural care were similar in both follow-up groups. Total costs were lower for nurse-led follow-up than for usual follow-up (€2,592 vs. €3,789), however, this difference was not

statistically significant. We concluded that, apart from medical issues and considerations with regard to quality of life/satisfaction of patients, costs could play a role in the decision making when considering involving nurses in counselling and treating patients after intentionally curative surgery for esophageal cancer (**Chapter 4C**).

Despite recent advances in the curative treatment of esophageal cancer, more than 50% of patients with esophageal cancer have inoperable disease at presentation. For these patients, only palliative treatment is possible. Self-expanding metal stents are frequently used for the palliation of esophageal obstruction because of inoperable cancer. A major drawback of stents is the risk of stent migration, which occurs in up to 20% of patients. To overcome this problem, a double-layered stent, the Niti-S stent, has been developed. Results from a prospective follow-up study in 42 patients treated with a Niti-S stent indicated that this new stent design provided good symptomatic relief of malignant dysphagia, and it effectively reduced recurrent dysphagia (**Chapter 5A**).

Another available new stent design is the fully covered Polyflex stent made of silicone. In a randomized study, we compared the Polyflex stent and the Niti-S stent with the worldwide most frequently used stent type, the Ultraflex stent. Between June 2004 and May 2006, 125 patients with dysphagia from inoperable esophageal and gastric cardia cancer were randomized to placement of an Ultraflex stent (n=42), Polyflex stent (n=41) or Niti-S stent (n=42). We compared the three stent types with respect to technical and functional outcome, complications, recurrent dysphagia and survival. All three stents offered the same degree of palliation of dysphagia. Although the complication rate was not different, recurrent dysphagia, particularly stent migration (Niti-S stent) and tissue in- or overgrowth (Polyflex stent), was less frequently observed during follow-up with these new devices (Ultraflex stent: 22 (52%) vs. Polyflex stent: 15 (37%) vs. Niti-S stent: 13 (31%); p=0.03). Median survival was 132 (Ultraflex stent), 102 (Polyflex stent) and 159 days (Niti-S stent), respectively. We concluded that Niti-S stents and Ultraflex stents are currently the preferred stent types over Polyflex stents in this patient group with inoperable esophageal or gastric cardia cancer. This is also based on the observation that placement of Niti-S stents or Ultraflex stents is technically less demanding than Polyflex stent placement (**Chapter 5B**).

In a retrospective study, we compared small and large diameter stents for improvement of dysphagia, and occurrence of complications and recurrent dysphagia. Three-hundred thirty-eight patients with dysphagia from obstructing esophageal or gastric cardia cancer were treated with either a small (22-24 mm; n=265) or large (28-30 mm; n=73) diameter Ultraflex stent, Gianturco-Z stent or Flamingo Wallstent. We found that large diameter stents reduced the risk of recurrent dysphagia due to stent migration, tissue in- or overgrowth, or food obstruction. Increasing the diameter in some stent types might, however, increase the risk

of stent-related complications to the esophagus, such as perforation, bleeding, etc. (**Chapter 5C**).

It has been suggested that the use of stents in the cervical esophagus is limited because of anticipated patient intolerance caused by pain and globus sensation. We retrospectively determined efficacy and safety of stent placement in 104 patients with a malignant obstruction close to the upper esophageal sphincter. Patients with primary esophageal carcinoma (n=66) or recurrent tumor after gastric tube interposition (n=38) within 8 cm of the upper esophageal sphincter were treated with a stent. Of these, 24 also had a fistula. The procedure was technically successful in 96% of patients. The fistula was sealed in 19 of 24 (79%) patients. At 4 weeks, dysphagia had improved from a median score of 3 (liquids only) to 1 (some difficulties with solids). Complications were seen in 34/104 (33%) patients, whereas recurrent dysphagia occurred in 29/104 (28%) patients. Globus sensation was experienced by 8% of patients, however in none of the patients stent removal was indicated (**Chapter 5D**).

In the **General Discussion** (**Chapter 6**), we concluded that this thesis demonstrates that nurse-led initiatives can be used to reconfigure care to make it more responsive to individual needs of patients, increase patient satisfaction, reduce the burden of hospital visits, and reduce the workload of physicians. Nurse-led care for designated tasks, such as diagnostic endoscopy and follow-up of particular patient groups, for example patients after resection of esophageal cancer, appears also to be more cost-effective than usual care given by physicians1.

Samenvatting

Wereldwijd worden jaarlijks ongeveer 400.000 patiënten gediagnosticeerd met slokdarmkanker. Indien de conditie van de patiënt een resectie toelaat en er geen doorgroei van de tumor in omgevende organen is of uitzaaiingen op afstand, is een chirurgische resectie de primaire behandeling voor slokdarmkanker.

Om een inventarisatie te maken van het huidige beleid van procedures tijdens follow-up na oncologisch gastrointestinale chirurgie, werd een enquête verricht door middel van een vragenlijst naar alle afdelingen Heelkunde in Nederland. De vragenlijst bevatte o.a. items over frequentie van follow-up bezoeken en aard en frequentie van diagnostische procedures na een chirurgische behandeling voor slokdarm-, maag-, alvleesklierkanker en kanker in het colon of rectum. Patiënten met colorectaal kanker en maagkanker werden voornamelijk in het eigen ziekenhuis behandeld; patiënten met slokdarmkanker en alvleesklierkanker werden veelal doorverwezen naar een tertiair centrum. Bloedonderzoek, colonoscopie en echo van de buik werden frequent uitgevoerd na een chirurgische behandeling voor colorectaal kanker. Bij de andere types gastrointestinale kanker werden alleen diagnostische procedures verricht als er sprake was van klachten en/of symptomen. Deze enquête liet zien dat follow-up na chirurgie voor colorectaal kanker vooral is gericht op het opsporen van recidieven en metachrone afwijkingen in het colon of rectum, terwijl er geen duidelijk beleid is ten aanzien van follow-up na chirurgie voor slokdarm-, maag- en alvleesklierkanker (**hoofdstuk 2**).

In de afgelopen 10 jaar hebben verpleegkundigen steeds vaker procedures verricht die daarvoor alleen voorbehouden waren aan artsen. Wij deden een literatuurstudie naar publicaties over gastrointestinale zorgverlening of behandeling en endoscopische procedures die door verpleegkundigen worden uitgevoerd. In totaal werden 19 publicaties geïdentificeerd waarin de verrichtingen van verpleegkundigen in de endoscopische praktijk waren geëvalueerd. Uit deze publicaties bleek dat verpleegkundigen in staat zijn om op een accurate en veilige wijze verschillende procedures uit te voeren, zoals gastroscopie, endo-echo, flexibele sigmoïdoscopie, video capsule endoscopie en assisteren bij het plaatsen van een percutane endoscopische gastrostomie (PEG) katheter. In twee studies werd beschreven dat verpleegkundigen op adequate wijze patiënten met Barrett oesophagus en inflammatoire darmziekte (IBD) konden begeleiden en/of behandelen. Patiënttevredenheid werd gemeten in 4 van de 19 studies en uitkomsten lieten zien dat patiënten tevreden waren met de door verpleegkundigen geleverde zorg. Daarnaast bleek dat sigmoïdoscopie en video capsule endoscopie door verpleegkundigen kosteneffectief was. Uitkomsten van deze literatuurstudie ondersteunen het inzetten en betrekken van verpleegkundigen bij diagnostische procedures en begeleiding/follow-up van patiënten met een chronische gastrointestinale aandoening (**hoofdstuk 3**).

We hebben onderzocht welke problemen patiënten ervaren na een slokdarmresectie en welke zorg zij verwachten van professionele zorgverleners. Dertig patiënten, bij wie de operatie niet langer dan 1 jaar geleden was verricht, werden gevraagd eenmalig een vragenlijst in te vullen. Patiënten werden gevraagd naar problemen die zij hadden ervaren op fysiek, psychologisch en sociaal gebied, en naar de zorg die zij voor deze problemen verwachtten. De meerderheid van de patiënten gaf aan dat specifieke fysieke problemen, zoals een veranderd eetpatroon en vermoeidheid, als zeer problematisch werd ervaren na de operatie. Ook psychische problemen, zoals een sombere stemming, angst voor metastasen en angst voor de dood waren items die deels hun leven beheersten. Patiënten verwachtten voornamelijk voor ziekte-gerelateerde fysieke problemen zorg en aandacht van professionele zorgverleners, terwijl psychosociale problemen vaker in eigen kring met familie en vrienden werden besproken. Ten slotte gaven patiënten gaven aan dat inbreng van verpleegkundigen tijdens de follow-up positief zou kunnen bijdragen aan het verwerken van hun problemen (**hoofdstuk 4A**).

In **hoofdstuk 4B** van dit proefschrift worden de resultaten beschreven van een gerandomiseerde studie waarin oncologisch verpleegkundige begeleiding in de thuissituatie wordt vergeleken met specialistische poliklinische controle van patiënten die een in opzet curatieve behandeling voor slokdarmkanker hebben ondergaan. Tussen januari 2004 en februari 2006 werden 109 patiënten gerandomiseerd voor poliklinische follow-up door een specialist of huisbezoeken door een gespecialiseerde verpleegkundige. Eindpunten van deze studie waren kwaliteit van leven, klinische uitkomsten, patiënttevredenheid en kosten. Patiënten werden geïncludeerd in 1 universitair en 1 algemeen ziekenhuis. De follow-up bezoeken vonden plaats op tijdstippen 6 weken, en 3, 6, 9 en 12 maanden na randomisatie. Tijdens het onderzoek werden longitudinale data verkregen van zowel de ziekte-specifieke als generieke kwaliteit van leven. Ziekte-specifieke kwaliteit van leven werd bepaald aan de hand van de EORTC QLQ-OES18. Dit is een specifieke vragenlijst voor patiënten met slokdarmkanker. Generieke kwaliteit van leven werd bepaald aan de hand van een vragenlijst voor kankerpatiënten, de EORTC QLQ-C30, de EQ-5D die een index score geeft aan een bepaald gezondheidsprofiel en een visuele analoge schaal bevat voor welbevinden, en de HAD schaal die de mate van angst en depressie aangeeft. Kwaliteit van leven data werden verkregen op de tijdstippen 6 weken postoperatief (baseline) en vervolgens 4, 7 en 13 maanden na de baseline meting. Gegevens over patiënttevredenheid werden verkregen op het tijdstip 7 maanden na de baseline meting. Tijdens de follow-up periode werd een verbetering gezien op de meeste schalen van de EORTC QLQ-OES18, de EORTC QLQ-C30 en de EQ-5D. Scores op de HAD schaal lieten zien dat patiënten niet angstig waren of depressieve gevoelens hadden. Gedurende de gehele follow-up periode was geen significant verschil te zien in kwaliteit van leven tussen beide follow-up groepen. Er werden geen verschillen gevonden in patiënttevredenheid. Wel waren partners van patiënten in de verpleegkundige follow-up groep meer

tevreden met dit type zorg. In totaal werden bij 11 (20%) patiënten in de verpleegkundige follow-up groep en bij 16 (29%) patiënten in de poliklinische follow-up groep metastasen ontdekt op een mediaan van 8 maanden na randomisatie. Veertien (13%) van deze patiënten waren binnen een jaar na de operatie overleden.

Tijdens de follow-up bezoeken werden het gebruik van medische voorzieningen en eventuele palliatieve behandelingen geregistreerd. De kosten van verpleegkundige follow-up waren significant lager dan die van poliklinische follow-up (€232 versus €453). Veruit het hoogst waren de kosten voor intramurale zorg voor beide types follow-up. De gemiddelde opnameduur in het ziekenhuis was 8,9 dagen voor patiënten in de verpleegkundige follow-up groep versus 17,8 dagen voor die in de poliklinische follow-up groep. Kosten van diagnostische procedures, additionele behandelingen en extramurale zorg waren in beide groepen gelijk. De totale kosten van verpleegkundige follow-up waren lager dan die van poliklinische follow-up (€2592 versus €3789), dit verschil was echter niet statistisch significant. Onze conclusie was dat, los van medische redenen en overwegingen wat betreft kwaliteit van leven of patiëntentevredenheid, kosten een rol kunnen spelen in de keuze om verpleegkundigen wel of niet te betrekken bij de begeleiding en behandeling van patiënten die een in opzet curatieve behandeling voor slokdarmkanker hebben ondergaan (**hoofdstuk 4C**).

Ondanks recente ontwikkelingen in curatieve behandelingen van slokdarmkanker, komt meer dan de helft van de patiënten niet meer in aanmerking voor een operatie, voornamelijk ten gevolge van aanwezigheid van metastasen of een slechte algemene conditie. Deze patiënten hebben bijna altijd een palliatieve behandeling nodig voor het verbeteren van voedselpassageklachten. Eén van de meest gebruikte palliatieve behandeling van passageklachten ten gevolge van slokdarmkanker is het plaatsen van een zelf-ontplooibare stent in de slokdarm. Een nadeel van stents is het risico van stent migratie, wat bij ongeveer 20% van de patiënten kan optreden. Om dit probleem te ondervangen, is een nieuwe stent ontwikkeld, de Niti-S stent. Deze stent heeft een geheel gecoverde binnenste lumen en een niet-gecoverde deel aan de buitenkant om respectievelijk weefselingroei en stent migratie te voorkomen. In een prospectieve follow-up studie werden 42 patiënten behandeld met een Niti-S stent. De studies liet zien dat dit nieuwe design een goede verbetering van passageklachten gaf en leidde tot een effectieve reductie van het optreden van hernieuwde passageklachten (**hoofdstuk 5A**).

Een ander nieuw design stent is de volledig gecoverde Polyflex stent, gemaakt van silicone. In een gerandomiseerde studie, werden de Polyflex stent en de Niti-S stent vergeleken met een stent die wereldwijd het meest wordt gebruikt, nl. de Ultraflex stent. Tussen juni 2004 en mei 2006 werden 125 patiënten met passageklachten op basis van een inoperabel slokdarmcarcinoom gerandomiseerd voor het plaatsen van een Ultraflex stent (n=42), Polyflex stent

(n=41) of Niti-S stent (n=42). Eindpunten van deze studie waren technische en functionele uitkomsten, het optreden van complicaties en hernieuwde passageklachten en survival. De drie stents gaven allen een goede verbetering van passageklachten. Er waren geen verschillen tussen de stents in het aantal opgetreden complicaties. Hernieuwde passageklachten, met name gerelateerd aan stent migratie (Niti-S stent) en weefselgroei (Polyflex stent), kwamen minder frequent voor bij de nieuwe stent designs (Ultraflex stent: 22 (52%) versus Polyflex stent: 15 (37%) versus Niti-S stent: 13 (31%); p=0,03). Survival (mediaan) was 132 dagen in de groep patiënten met een Ultraflex stent, 102 dagen in die met een Polyflex stent, en 159 dagen in die met een Niti-S stent. Onze conclusie was dat het plaatsen van een Niti-S stent of een Ultraflex stent de voorkeur heeft boven de Polyflex stent bij patienten met een inoperabel slokdarmcarcinoom. Dit is mede gebaseerd op het feit dat het plaatsen van een Niti-S stent of Ultraflex stent technisch makkelijker is dan het plaatsen van een Polyflex stent (**hoofdstuk 5B**).

In een retrospectieve studie werden stents met een kleine diameter vergeleken met die met een grote diameter wat betreft verbetering van passageklachten en het optreden van complicaties en hernieuwde passageklachten. Driehonderd acht en dertig patiënten met passageklachten ten gevolge van inoperabel slokdarmkanker waren behandeld met een kleine diameter (22-24 mm; n=265) of grote diameter (28-30 mm; n=73) Ultraflex stent, Gianturco-Z stent of Flamingo Wallstent. In de groep patiënten met een grote diameter stent was het risico op het optreden van hernieuwde passageklachten, veroorzaakt door migratie, weefselgroei of voedselobstructie, lager dan bij kleine diameter stents. De grootte van de diameter gaf bij sommige stents echter een verhoogd risico op stent-gerelateerde complicaties aan de slokdarmwand, zoals perforatie, bloeding, etc. (**hoofdstuk 5C**).

Over het algemeen wordt aangenomen dat het plaatsten van stents hoog in de slokdarm slechts gelimiteerd mogelijk is, omdat patiënten dit niet goed kunnen verdragen en klagen over pijn en globus sensatie. Wij verrichtten een retrospectieve studie, waarin werd gekeken naar de effectiviteit en veiligheid van stentplaatsing bij 104 patiënten met een kwaadaardige obstructie dicht bij de bovenste slokdarm sphincter. De patiënten bij wie een stent was geplaatst hadden een primaire maligniteit in de slokdarm (n=66) of een lokaal recidief na slokdarmresectie (n=38) binnen 8 cm van de bovenste slokdarm sphincter. Vier en twintig patiënten hadden ook een fistel naar de luchtwegen. Bij 96% van de patiënten lukte het om een stent te plaatsen; de fistels van 19/24 (79%) patiënten waren succesvol afgedekt door de stent en er was een verbetering te zien in passageklachten. Bij 34/104 (33%) patiënten traden er complicaties op en bij 29/104 (28%) patiënten hernieuwde passageklachten. Hoewel 8% van de patiënten klaagden over globus sensatie, was het bij deze patiënten niet nodig om de stent te verwijderen (**hoofdstuk 5D**).

In de **General discussion (hoofdstuk 6)** werd geconcludeerd dat de zorg van patiënten met een maligniteit meer zou kunnen worden afgestemd op de individuele zorgbehoefte van de patiënt, wat kan leiden tot verhoging van de satisfactie bij patiënten, minder poliklinische bezoeken en verlaging van de werklast van artsen. Verpleegkundig specialistische zorg, zoals diagnostische endoscopie en follow-up van specifieke patiëntengroepen, bijvoorbeeld na slokdarmresectie, blijkt effectief te zijn en leidt tot kostenreductie.

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CURRICULUM VITAE

Elisabeth Maria Lutgardis (Els) Verschuur werd op 23 juni 1960 geboren te Doesburg. Ze voltooide haar VWO aan het Pius-X College te Almelo en ging in 1978 HBO-Verpleegkunde studeren aan de Twentse Akademie voor Gezondheidszorg te Hengelo (O). Na de HBO-V is ze gaan werken in onder andere de Thuiszorg, het Ziekenhuis en in de Kraamzorg. In 1994 heeft ze de Leraren Opleiding voor Verpleegkundigen (LOV) afgerond, en ging ze als docent aan de slag. Eerst bij een inservice opleiding voor A-verpleegkundigen en later, na de herzieningen in het gezondheidszorgonderwijs, in het MBO bij de opleiding voor Verpleegkundige niveau 4. Tijdens deze periode heeft ze zich veel beziggehouden met leerplanontwikkeling en onderwijsvernieuwing. In augustus 1995 is ze gestart met de studie Gezondheidswetenschappen, studierichting Verplegingswetenschappen, te Utrecht. Tijdens haar studie voltooide ze een afstudeeronderzoek over specialistische thuiszorg bij het NIVEL.

Van januari 2002 tot mei 2003 werkte ze als docent bij de Hogeschool Arnhem-Nijmegen (HAN) en Saxion Hogeschool Deventer. Ook daar heeft ze zich, naast het verzorgen van onderwijs, weer beziggehouden met leerplanontwikkeling. In mei 2003 startte ze haar promotieonderzoek bij de afdeling Maag-, Darm- en Leverziekten van het Erasmus MC te Rotterdam, onder begeleiding van haar co-promotor dr. P.D. Siersema en haar promotoren prof.dr. E.J. Kuipers en prof.dr. E.W. Steyerberg. Het onderzoek betrof verpleegkundige follow-up en palliatieve zorg voor patiënten met slokdarmkanker en vormde de basis voor dit proefschrift. In juni 2007 is ze gaan werken als onderzoeker bij de Unit Innovaties in de Zorg van het Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde te Utrecht. Daar houdt ze zich bezig met onderzoek op het gebied van spoedeisende zorg, en verzorgt ze onderwijs voor studenten Geneeskunde.

Dankwoord

Ruim vier jaar geleden kwam ik voor de eerste keer naar het Erasmus MC voor een sollicitatiegesprek. Na het gesprek had ik er weinig vertrouwen in dat ik de openstaande promotieplaats zou kunnen bemachtigen. Allereerst kwam ik te laat; niets voor mij, maar de NS liet me weer eens in de steek. Vervolgens stond ik na ongeveer 20 minuten alweer bij de lift. Ik had nog nooit zo'n kort sollicitatiegesprek gehad, waarin zo weinig naar mijn kennen en kunnen werd gevraagd. De afstand, daar ging het voornamelijk over: zou het me lukken om dagelijks van Dieren naar Rotterdam te komen? We zijn nu vier jaar verder en het antwoord is: Ja, het is me gelukt.

Op 1 mei 2003 ben ik begonnen met mijn promotietraject. Alle begin is moeilijk, maar dit begin in het bijzonder. Op mijn eerste werkdag overleed mijn neef Harrie. Ma, die jarenlang een fantastische vervanger van mijn moeder is geweest, overleed een week later op 7 mei. De gedachte dat ze er niet meer is, stemt me nu nog steeds verdrietig. Daarnaast stapte ik de wereld van Geneeskunde binnen, die, hoewel verwant, toch heel anders is dan de wereld van Verpleegkunde. We spreken misschien wel dezelfde taal, maar zeggen niet altijd hetzelfde. Het was wel even wennen, maar na een paar maanden had ik mijn weg gevonden, de doelen waren duidelijk en ik was vastbesloten die doelen te halen.

Er zijn zoveel mensen geweest die ik in mijn onderzoekstijd heb ontmoet. Mijn grootste dank gaat uit naar alle patiënten die, vaak zonder aarzelen, hebben ingestemd om deel te nemen aan mijn studies. Ik voelde me bevoorrecht dat ik lief, maar helaas ook veel leed met hen mocht delen. De hoop op genezing, de voorzichtige blijdschap als het goed blijft gaan, het doorzettingsvermogen, het niet op willen geven, ook als het een verloren strijd blijkt te zijn, het verlies en het afscheid van het leven; hoeveel kan een mens aan.

Grote dank gaat uit naar dr. P.D. Siersema, vier jaar lang mijn begeleider geweest en nu afdelingshoofd en hoogleraar in het UMC Utrecht. Prof.dr. Siersema, Peter, je was een goede, maar soms ook een lastige "heer om te dienen". Je enthousiasme en gedrevenheid hebben me enorm gestimuleerd, en dat was goed. Lastig was dat je de druk soms behoorlijk kon opvoeren. Ik leg de lat hoog; jij legt hem altijd hoger. Het kan en moet altijd beter en het gaat dan ook altijd beter. En zie hier het resultaat: het is een prachtig proefschrift geworden. Ik ben er in ieder geval heel erg trots op. Wat hebben we veel gedaan en wat heb ik veel van je geleerd. Al je inspanningen en steun tijdens mijn promotieonderzoek heb ik zeer gewaardeerd. Dank je wel voor je begeleiding, je vertrouwen, je kritische blik en voor je hulp bij het tot stand komen van dit proefschrift.

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voor elkaar kreeg. Prof.dr. E.W. Steyerberg, Ewout, goed onderzoek is onlosmakelijk verbonden met goede statistiek, en daar sta jij garant voor. Ik kon altijd bij je terecht als ik vragen had of als ik onzeker was of ik de juiste analyses had uitgevoerd. Dank je wel voor je steun.

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Wat kan ik zeggen over de Barrett-groep. Het is een groep van allemaal heel hardwerkende, zeer gemotiveerde en getalenteerde collega's. Hoewel de bindende factor de slokdarm was, was iedereen bezig met zijn eigen specifieke onderzoek. De meetings gingen vaak over basaal onderzoek; iets wat, ook na vier jaar, nog steeds ver van mij afstaat. Desondanks heb ik toch veel geleerd. Collega's van de Barrett-groep: ooit komt er een tijd dat iemand eindelijk ontdekt waarom een normale cel in de slokdarm 'besluit' om een tumorcel te worden. Misschien is die iemand wel één van jullie. Heel veel succes!

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In memoriam:

Mama en Papa Verschuur
Ma en Pa Klein Haarhuis
Mama Slingerland

Lonny Slingerland
Truus Kroft - Klein Haarhuis
Harrie Workel

Dieren, 13 juli 2007