# Changes in diagnostic and treatment strategies of oesophageal cancer in the period from 2001 to 2009: a survey in the Netherlands

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***Background*** **In 2005, national guidelines on the diagnosis, staging and treatment of oesophageal cancer were published. We investigated whether staging and treatment strategies of oesophageal cancer had changed over the last decade and indeed followed these guidelines.**

***Materials and methods*** **In 2001, a questionnaire investigating staging and treatment strategies for oesophageal cancer was sent to Dutch clinicians (response rate 64%). In 2009, the same questionnaire (response rate 41%) was repeated, thus enabling comparison of staging and treatment strategies for oesophageal cancer between 2001 and 2009 and comparing this with the nationwide guidelines of 2005.**

***Results*** **The advice to use endoscopic ultrasound for staging was followed by the majority of clinicians [84% in 2009 compared with 58% in 2001 ($P<0.001$)], whereas positron emission tomography scanning was used by almost half of clinicians (44% in 2009, not asked in 2001). There was a strong support for the use of neoadjuvant chemoradiation in 2009 (68% preferred this treatment for a young patient in good condition without metastases), whereas the Dutch guidelines did not recommend routine use of neoadjuvant treatment in 2005. Stent placement for palliation of dysphagia was reduced [from 92% in 2001 to 27% in 2009 ($P<0.001$)] due to an increased use of other palliative measures, including brachytherapy. An increased use of chemotherapy (19%) or chemoradiation (39%) was noticed in younger patients (<55 years) with metastatic disease.**

***Conclusion*** **Major changes in staging and treatment strategies were observed in patients with oesophageal cancer over the last decade. Although these changes in staging strategies were in concordance to the guidelines introduced in 2005, treatment strategies with curative intent were more often diverse in 2009 and not following guidelines. This suggests that in a rapidly evolving field as oncology, guideline recommendations on treatment should be updated frequently to reflect state-of-the-art knowledge with implementation of results of clinical studies.** ***Eur J Gastroenterol Hepatol*** **24:126–133 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

The management of oesophageal cancer is challenging with a rapidly rising incidence and still poor survival. The incidence of oesophageal cancer in the Netherlands was 10.1/100.000 inhabitants in 2007 compared with 4.6/100.000 at the start of the national Dutch registration in 1989, an increase of 5% per year [1].

In 2001, we performed a survey investigating staging and treatment strategies of oesophageal cancer by Dutch clinicians involved in the care of these patients [2]. It was concluded that a variety of staging and treatment strategies were operational. Hence, in 2005 evidence-based nationwide guidelines on the 'Diagnosis, Staging and Treatment of Oesophageal Cancer' was developed, with input by all medical and paramedical disciplines involved in the care of patients with oesophageal cancer [3]. A summary of the guidelines is presented in Box 1. These Dutch guidelines were based on the 6th edition of the Tumor Node Metastasis (TNM) classification [4]. In 2009, a modified questionnaire on staging and treatment strategies was sent to Dutch clinicians to investigate whether the nationwide guidelines were actually followed. The aims of this study were to investigate whether staging and treatment strategies of oesophageal cancer had changed between 2001 and 2009 and whether clinicians involved in the diagnosis, staging and treatment of oesophageal cancer had changed their clinical practice based on the guidelines that were published in 2005.

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**Box 1**

**MAIN CONCLUSIONS OF THE DUTCH GUIDELINES FOR THE DIAGNOSIS, STAGING AND TREATMENT OF OESOPHAGEAL CANCER 2005 [BASED ON THE 6TH EDITION OF THE TUMOR NODE METASTASIS (TNM) CLASSIFICATION]**

*Diagnostic and staging workup*

After diagnosing oesophageal carcinoma with endoscopy and histopathological proof, the next staging procedures are indicated:

- Computer tomography of the thorax and abdomen for lymph node metastases in the mediastinum (N stage), celiac trunc (M stage) and/or distant metastases in the lung, liver and adrenal glands (M stage).
- External ultrasound (US) for cervical lymph nodes (M stage).
- Endoscopic US for locoregional tumour staging (T status) and regional lymph nodes (N or M stage).
- Positron emission tomography scanning should be considered for T3 stage oesophageal cancer for diagnosing distant metastases.
- In case of relevancy for treatment, fine-needle aspiration of suspected lymph nodes should be performed using endoscopic US or external US.
- Bronchoscopy with brush cytology should be considered in advanced oesophageal cancer in the proximal oesophagus to exclude airway invasion.

*Treatment*

Treatment of oesophageal cancer depends on TNM stage, the condition of the patient including comorbidity and/or patient's preferences and professional expertise. The treatment recommendations for the different patient vignettes are discussed in the Results section.

*Palliative treatment to relieve dysphagia*

- On the basis of the faster relief of dysphagia, stent placement is advised for patients with a life expectancy less than 6 weeks.
- Brachytherapy alone or in combination with external beam radiation is advised for patients with dysphagia and a life expectancy of more than 3 months.

## Materials and methods

In 2001, a written questionnaire was sent to Dutch clinicians (internists, gastroenterologists and surgeons) working in the field of gastroenterology. A total of 426 (64%) questionnaires were returned [2]. In 2009, a modified questionnaire was sent by email with a response rate of 41% ($n = 231$). The questionnaire included seven multiple-choice questions (the questionnaire can be accessed at *http://www.utrechtdigestivecenter.nl/wrapper.php?menuid=5&submenuid=11&subsu*). The first four questions asked for general characteristics of the responders, their clinical specialization, the hospital of employment (categorized in university or general), the number of new patients with oesophageal cancer seen annually, and whether such patients were generally treated in the clinician's own hospital or were referred to another (university) hospital. Question 5 investigated the type of staging procedures and the frequency with which these were applied in the patients. Answering categories were: in 0–10% of the patients, 10–49%, 50–90% and in more than 90% of the patients. In question 6, the participants were asked to make a judgement on the treatment of a patient with oesophageal cancer presenting with dysphagia for several clinical scenarios. Patient vignettes were chosen with varying variables, such as age (55 or 80 years), general health (good or poor) and tumour stage (locoregional tumour ingrowth or metastases). The final question investigated which types of palliative treatments were used for treating malignant dysphagia with the same answering categories as question 5.

A few modifications were made in the questionnaire compared with the one that was used in 2001. In question 5, we added positron emission tomography (PET) scanning and bronchoscopy to the staging procedures. In question 6, we added surgery with neoadjuvant treatment, chemoradiation as definitive treatment and placement of a percutaneous endoscopic gastrostomy (PEG) to the possible answers and deleted repeated dilation. In question 7, we added PEG placement to the palliative treatments.

### Statistics

Descriptive statistics were used to list information of the clinicians that participated in our surveys with regard to clinical registration, academic position, number of patients treated and proportion of referral for staging

and treatment. We then compared differences in staging procedures and palliative treatments using the above-mentioned six clinical vignettes between 2001 and 2009 with the $\chi^2$-test. As more answer categories were added to the patient vignettes, the differences in treatment procedures were not statistically compared. We considered $P$ value of less than 0.05 to be statically significant. Statistical analyses were conducted with the SPSS statistical software, version 15.0 (SPSS Inc. Headquarters, Chicago, Illinois, USA).

## Results

After excluding clinicians who were not treating patients with oesophageal cancer as well as retired clinicians, 336 questionnaires in 2001 and 180 in 2009 were available for analysis. Characteristics of the clinicians with completed questionnaires are shown in Table 1.

### Staging

In 2009, endoscopic ultrasound (EUS) and computer tomography of the thorax and abdomen were more frequently used for staging: 84% of the clinicians requested EUS in more than 50% of their patients compared with 58% in 2001 ($P \leq 0.001$; Fig. 1). PET scanning was often used with 44% of clinicians using it in more than 50% of their patients in 2009 (not asked in 2001). The increased experience and availability of EUS and PET scan will have added to these results. Abdominal ultrasound and laparoscopy were almost no longer used for staging in 2009. These changes are in concordance with the recommendation of the Dutch guidelines (outlined in Box 1), with particularly EUS being recommended for locoregional tumour staging (T status) and regional and celiac lymph nodes (N or M stage), but abdominal ultrasound no longer being recommended for diagnostic workup. PET scanning was recommended in case of suspicion of a T3 oesophageal cancer according to the guidelines.

**Table 1 General characteristics of the clinicians with completed questionnaires in 2001 ($n=336$) and 2009 ($n=180$)**

| | 2001 *N* (%) | 2009 *N* (%) |
|---|---|---|
| Clinicians registration | | |
| Internal medicine/medical oncology | 111 (33) | 58 (32) |
| Gastroenterology | 117 (35) | 50 (28) |
| Surgery | 108 (32) | 54 (30) |
| Radiotherapy | | 17 (9) |
| Other | | 1 (1) |
| Hospital | | |
| University | 75 (22) | 44 (24) |
| General | 259 (77) | 136 (76) |
| Both | 2 (1) | |
| Number of new patients treated by clinician annually | | |
| 0–5 | 94 (28) | 36 (20) |
| 5–20 | 197 (59) | 87 (48) |
| 20–50 | 32 (10) | 41 (23) |
| >50 | 13 (4) | 16 (9) |
| Hospital where staging and treatment of patients is performed | | |
| Never referred to other (university) hospital | 153 (46) | 91 (51) |
| Sometimes (<50%) to other (university) hospital | 104 (31) | 36 (20) |
| Mostly (>50%) referred to other (university) hospital | 44 (13) | 27 (15) |
| Always referred to other (university) hospital | 33 (10) | 26 (14) |

### Treatment

A shift in the opinion of treatment options was observed between 2001 and 2009 with regard to the clinical case vignettes (Fig. 2).

#### *A 55-year-old participant in good condition without metastases*

In 2001, almost all clinicians (99%) chose primary surgery as the best treatment option for this patient, whereas in 2009 68% chose neoadjuvant chemoradiation and surgery (Fig. 2a). This is in line with the 2005 guideline that recommended neoadjuvant chemoradiation, but only within a research setting.

#### *A 55-year-old patient in good condition with metastatic disease*

For a patient with a mid or distal oesophageal tumour and positive cervical lymph nodes, the majority of clinicians chose palliative treatment in 2001 (55% stent placement). In 2009, 19% opted for chemotherapy and 39% for chemoradiation (Fig. 2b). Although the guidelines recommended palliative treatment to improve dysphagia, this was followed by only 35% of clinicians in 2009.

#### *A 55-year-old patient with locoregional tumour ingrowth (T4, not specified)*

Thirty-nine percent of clinicians preferred external beam radiation (EBRT) in combination with brachytherapy for cT4 tumours in 2001 compared with 41% that favored neoadjuvant chemoradiation plus surgery and 37% definitive chemoradiation in 2009 (Fig. 2c). The 2005 guideline did not recommend a standard treatment for cT4 tumours due to a lack of evidence available, but it was recommended to take the patient's condition and tumour characteristics into account when deciding on the treatment modality. For this patient in a good clinical condition, it was advised to consider chemoradiation.

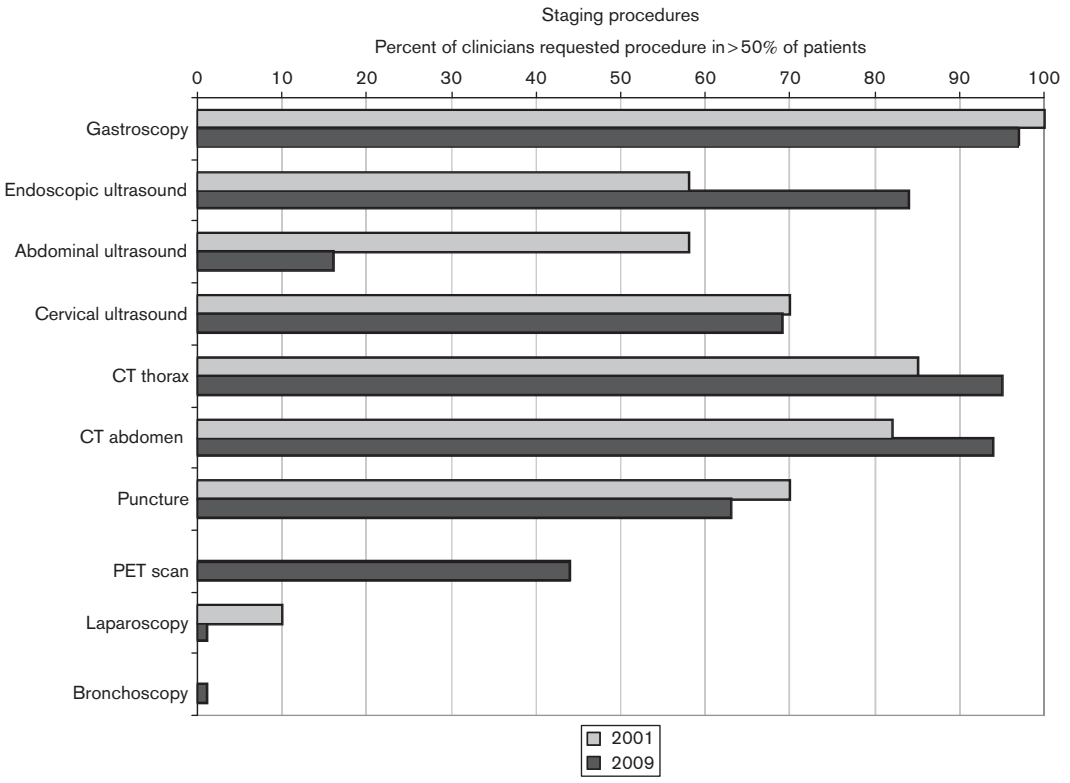
#### *55-year-old patient in poor condition (severe chronic obstructive pulmonary disease) without metastases*

For the same patient in a poor clinical condition (severe chronic obstructive pulmonary disease), stent placement (40%) or EBRT with brachytherapy (31%) were the main modalities opted for in 2001 compared with chemoradiation (29%), brachytherapy alone (27%) or stent placement (13%) in 2009 (Fig. 2d). The guidelines recommended chemoradiation, which was chosen by only 29% of clinicians.

#### *80-year-old participant in good condition without metastases*

For this patient, 53% of respondents chose for surgery in 2001. This was also true for 2009 (49%), but another 21% would combine surgery with neoadjuvant chemoradiation

**Fig. 1**




Staging procedures chosen by clinicians for more than 50% of their patients with oesophageal cancer in 2001 and 2009. CT, computed tomography; PET, positron emission tomography.

(Fig. 2e). Surgery was recommended by the guidelines, which was followed by the majority of clinicians with or without neoadjuvant therapy.

#### *80-year-old patient in good condition with metastatic disease*

If the same patient had cervical lymph node metastasis, most clinicians chose a palliative option. Wherein 2001 mostly stent placement (58%) was chosen, a shift towards the use of brachytherapy (31%) or EBRT (26%) was seen in 2009 (Fig. 2f). The guidelines advised palliative treatment with brachytherapy for this patient.

#### Palliative procedures to relieve dysphagia

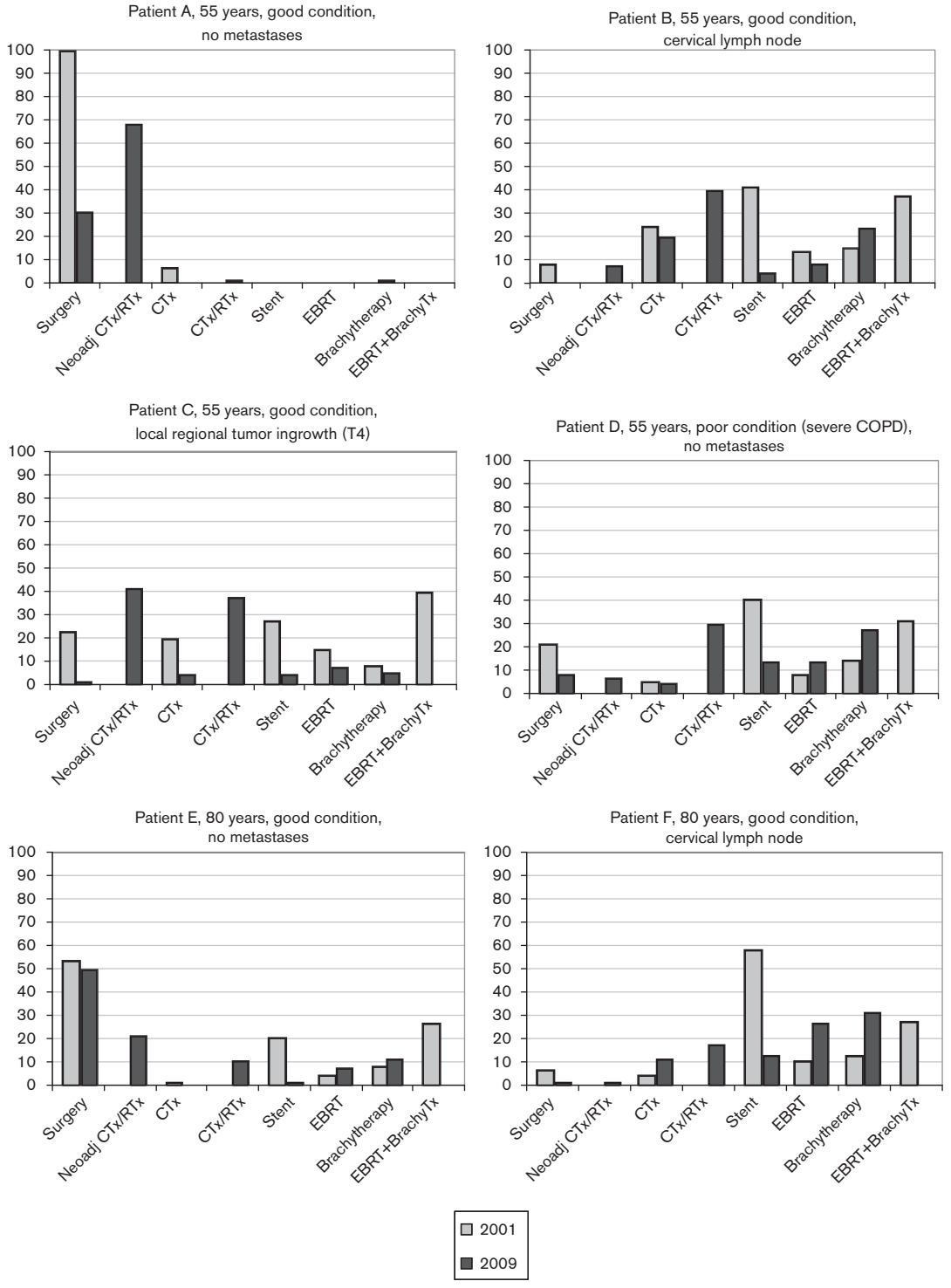
Stent placement was by far the most commonly used treatment to palliate dysphagia in 2001 (Fig. 3). This had significantly reduced in 2009 from 92 to 27% of clinicians treating more than 50% of their patients with stent placement ($P < 0.001$). The combination of EBRT and brachytherapy was also less frequently used (17 vs. 10% in 2009, $P < 0.04$). In 2009, more variation in palliative treatments was noticed, with 55% using brachytherapy in 10–50% of patients, 58% stent placement in 10–50% of patients, and 46% EBRT in 10–50% of their patients. Dilation and PEG placement was used for a small minority of patients. The choices for palliative treatment had changed in concordance to the recommendations in the guidelines (outlined in Box 1). Stent placement and radiotherapy (brachytherapy alone or in combination with EBRT) were almost equally used as both treatments were recommended depending on the life expectancy of the patient.

## Discussion

This study shows major changes in staging and treatment strategies in patients with oesophageal cancer over the last decade. Changes in staging strategies were in concordance to the guidelines introduced in 2005. In contrast, current treatment strategies were more often diverse and did not always follow the guidelines.

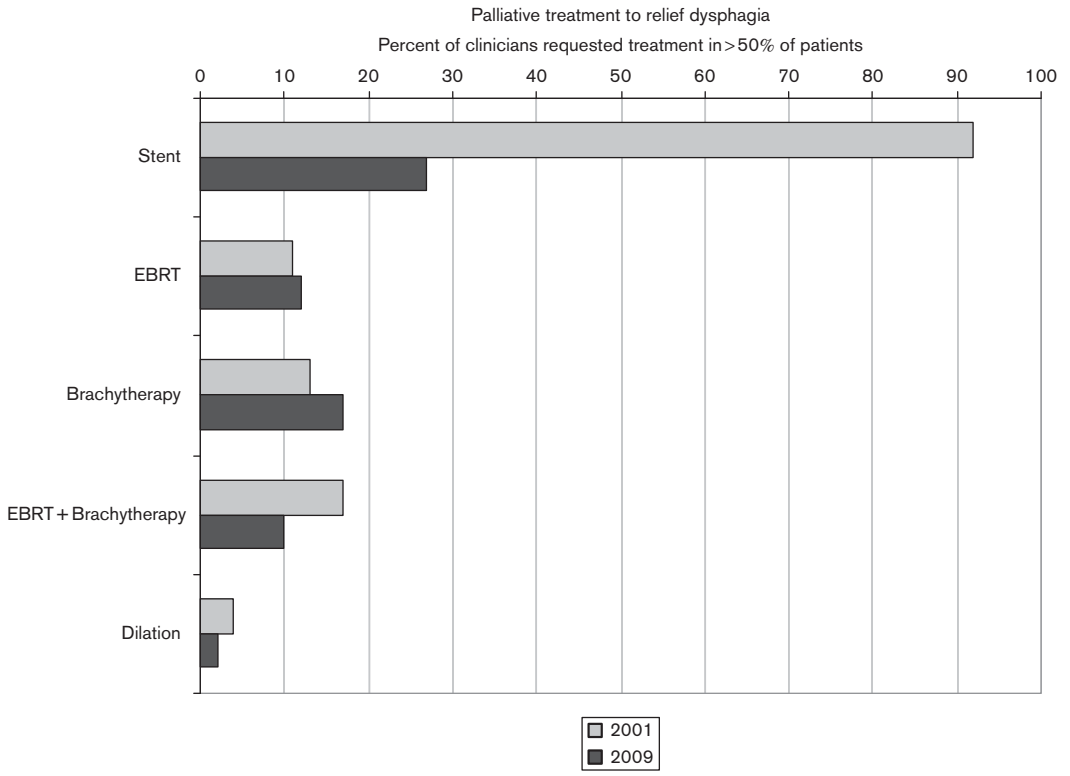
Staging of oesophageal cancer is of major importance to differentiate between early and advanced disease to guide treatment and predict outcome. Recent studies have shown that EUS has a good sensitivity and specificity in diagnosing T and N stage of oesophageal cancer and, in combination with fine needle aspiration, improves prediction of correct N stage [5]. EUS is therefore strongly recommended in the diagnostic workup. In this study, this advice was taken on as demonstrated by a

**Fig. 2**




Treatments chosen for different patient vignettes with oesophageal cancer. BrachyTx, brachytherapy; COPD, chronic obstructive pulmonary disease; CTx, chemotherapy; EBRT, external beam radiotherapy; Neoadj CTx/RTx, neoadjuvant chemoradiation.

**Fig. 3**




Palliative treatments chosen to relief dysphagia in patients with oesophageal cancer in 2001 and 2009. EBRT, external beam radiotherapy.

major increase in the application of EUS. The optimal treatment of resectable oesophageal cancer has long been surgery alone. A major discussion in the last decade has been whether these results could be improved by adding neoadjuvant chemotherapy or chemoradiation to surgery. In the Dutch guidelines, preoperative chemoradiation was supported, but it was advised to use it only within a research setting, because strong evidence was not available at that time. Since then, new randomized controlled trials and meta-analysis have shown that preoperative (cisplatin-based) chemotherapy and concurrent radiotherapy followed by oesophagectomy is the preferred treatment modality. Neoadjuvant chemoradiation and surgery will also be advised in the upcoming revision of the Dutch guidelines [6–8].

Patients with locoregional tumour ingrowth (T4) have a poor prognosis. Randomized trials comparing different treatment modalities are still not available. Oesophagectomy is only indicated in selected cases and may well improve survival [9]. A standard treatment is not available and depends on patient and tumour characteristics. Chemoradiation may result in longer palliation and even a resection with curative intent can be considered if the tumour is responding well to the treatment [10–13]. Our study demonstrates a wide variation in treatment modalities applied, which emphasizes that clinical trials comparing different treatment modalities are warranted. Recent guidelines recommend chemoradiation if condition of the patient is allowing this intensive treatment. This might well result in a more uniform treatment strategy. For metastatic disease, the use of chemotherapy as palliative treatment is common practice, unfortunately clinical evidence is still lacking [14].

The choices for a palliative treatment modality to relieve dysphagia have changed in concordance with the guidelines. This is at least partly due to a large multi-centre, randomized trial performed in the Netherlands comparing stent placement with brachytherapy for palliation of dysphagia, showing a better long-term effect of the latter compared with stent placement [15]. In clinical practice, the palliative treatment choice mainly depends on the life expectancy of patients. It has been reported that patients with a relatively better prognosis should be treated with brachytherapy, whereas in the case of an expected short prognosis, the primary choice should be stent placement [15,16].

An important conclusion that came out of this study is that major changes have taken place in the treatment of oesophageal cancer in the last decade. A frequently heard

complaint is that oncology guidelines are not updated frequently enough and therefore cannot always be adhered to [17,18]. This study illustrates that regular updates, especially for the treatment of (oesophageal) cancer, are of utmost importance to aid physicians and patients in choosing the most optimal treatment on the basis of the best available evidence. The 2005 guidelines on oesophageal cancer were recently revised and published online in December 2010 [19]. This national guideline is highly comparable with the guidelines of the National Comprehensive Cancer Network, version 2.2011 [20]. One addition to the diagnostic workup of the National Comprehensive Cancer Network guidelines is the advice to test for HER2-Neu expression for metastatic disease for considering trastuzumab as palliative treatment. Curative and palliative treatment advices were similar.

Our study has several strengths but also some limitations. This is a descriptive study on changes in staging and treatment strategies in the Netherlands. Unfortunately, it was not possible to include the same respondents from the 2001 questionnaire for the survey in 2009 because of anonymity. Nonetheless, the percentages of respondents among surgeons, gastroenterologists and internal medicine physicians were similar comparing 2001 with 2009. The same was true for professionals working in a university hospital or a general hospital. This suggests that the respondents were representative for the Dutch medical community. Both questionnaires used the 6th edition of the TNM classification. In 2010, the revised 7th edition became available, with in particular changes in the T4 classification, N subclassification, M stage and separate stage groupings for squamous cell carcinoma and adenocarcinoma [21]. As both questionnaires used the 6th TNM classification, this did not affect our results. Some changes were made in the 2009 questionnaire due to the emergence of new diagnostic tools and treatment strategies. Robust statistical analyses were therefore not always possible. However, this descriptive study gives sufficient information to draw some conclusions and recommendations. Finally, this questionnaire did not cover staging and treatment of early stage oesophageal cancer (T1m1–3). It is, however, unlikely that this will have affected the main conclusions of our study, as this patient category is only small (< 5%) compared with the vast majority of patients presenting with more advanced disease.

In conclusion, major changes in staging and treatment strategies occurred in patients with oesophageal cancer over the last decade. For staging, EUS, and to a lesser degree PET scanning, has become the standard of care. Abdominal ultrasound has largely disappeared in concordance with the Dutch guidelines. Treatment has shifted from single modality (surgery) towards multimodality with a prominent role of neoadjuvant chemoradiation. Palliative treatment strategies are nowadays more diverse. The currently used treatment modalities often do not follow guidelines, suggesting that treatment strategies are rapidly evolving and probably are being used on a more individualized basis. Hence, oncology guideline recommendations should be adapted more frequently and the feasibility of guideline adaptation as an ongoing process should be studied.

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### Conflicts of interest

There are no conflicts of interest.

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