Oesophageal cancer

Staging, Surgery and Survival

A.K. Talsma

Colofon

Oesophageal cancer: Staging, Surgery and Survival
Proefschrift Erasmus Universiteit Rotterdam
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De schilders van kunstkring *De Ploeg* hadden het weidse Groninger landschap tot hun belangrijkste onderwerp. De karakteristieke 'Ploeg-landschappen' ontstonden: hoge horizonten en in de verte verdwijnende wegen en sloten. Het is waarschijnlijk deze terugkerende compositie waardoor ik iedere keer in de Ploeg-schilderijen de anatomische overgang tussen slokdarm en maag lijk te zien. Een beroepsdeformatie waarschijnlijk.

Op de voorkant is afgebeeld het schilderij *Dijk langs het Reitdiep* van Jan Altink. Verder zijn weergegeven: *De rode boerderij*, *Gezicht op het Reitdiep*, *Koopvrouw op landweg* (Jan Altink), *Boerderij Menkema*, *Gezicht op Garnwerd* (Johan Dijkstra), *Groninger landschap met kanaal* (Jan Wiegers), *Lanschap Zuidwolde* (Jannes de Vries), *Dijk en wad* (Jan Lucas van de Baan).

Ben ik de enige die iedere keer weer die gastro-oesophageale overgang ziet?

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Promotor:

Prof.dr. J.J.B. van Lanschot

Overige leden:

Prof.dr. M.J. Bruno
Prof.dr. J.T.M. Plukker
Prof.dr. E.W. Steyerberg

Copromotor:

Dr. B.P.L. Wijnhoven

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Chapter 1

General introduction and outline of the thesis

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INTRODUCTION

Oesophageal cancer is a challenging malignancy of cancer for many reasons, requiring the interdisciplinary approach of e.g. surgeons, gastroenterologists, medical and radiation oncologists, intensivists, radiologists, nuclear physicians, pathologists, dieticians and special care nurses. Since the first successful oesophagectomy for cancer was performed in 1909 in the United States by Franz Torek (a son of German U.S. immigrants), many improvements have been made in the treatment of oesophageal cancer. Postoperative mortality rates have decreased from 30% in the 1950s-60s to 13 % in the 1980s and less than 5 % nowadays in experienced hands. Surgical techniques have been refined and multimodality treatment has become the standard of care. Other recent developments include the introduction of nationwide quality audits. Although these developments have contributed to an increased quality of care, there are some persevering "failures" that persist in the treatment of oesophageal cancer and its complications. This leaves room for ongoing research into this still devastating disease.

In the first place involved physicians are faced with the aggressive natural behaviour of this disease with early lymphatic and distant dissemination. Most patients present with advanced disease, leaving only 30-40% of patients suitable for potentially curative treatment. Even after radical surgery many patients suffer from early recurrence, suggesting a "failure to stage" by current staging modalities. Although long-term survival rates have improved, there is still a "failure to cure" in more than half of the patients who undergo surgery, which has led to the recent implementation of (neo-)adjuvant chemotherapy with or without radiotherapy.

Secondly, there is the surgical resection. For many years surgery alone, without preceding neoadjuvant therapy, had the disadvantage of "failure to resect" leading to involved surgical resection margins. The required oncological radicality in close vicinity to several vital anatomical structures (heart, aorta, trachea) makes an oesophagectomy probably one of the most challenging procedures in surgery. Moreover the continuity of the upper gastrointestinal tract has to be reconstructed, with its associated postoperative morbidity and even mortality, especially when complications cannot be treated early and appropriately ("failure to rescue").

In the third place there is a striking rise in the incidence of oesophageal (adeno-) carcinoma, especially in the Western hemisphere, which is only partly understood. This "failure to prevent" is beyond the scope of the present thesis.

Outline of the thesis

This thesis includes clinical studies that address the themes as mentioned above and focus on recent developments in surgery (Part I), staging (Part II) and survival (Part III) of oesophageal cancer patients.

PART I – GOALS OF SURGICAL THERAPY FOR OESOPHAGEAL CANCER

Although during the past decade multimodality treatment has become standard of care, surgery is still a crucial part in the potentially curative treatment of oesophageal cancer patients. In **Chapter 2** an overview of the literature on goals of surgical therapy is presented including radical resection, appropriate lymph node retrieval, gastrointestinal reconstruction and the limitation of the related morbidity and mortality. Two different surgical approaches are discussed: the transthoracic oesophagectomy (TTO) with extended lymphadenectomy of the middle and lower mediastinal nodes versus the less invasive transhiatal oesophagectomy (THO), in which only the perioesophageal nodes and the nodes in the upper abdomen are removed. Arguments for more extensive surgery are optimal staging, better locoregional control and thus potentially improved cure rates. However, four randomised controlled trials comparing TTO and THO have been published which have failed to demonstrate significant differences between the two approaches. The same debate is going on for the extent of lymphadenectomy: a more extended lymph node dissection contributes to the accuracy of staging the disease, but there is still no evidence whether it really contributes to an improved survival. In **Chapter 2** also an overview of the optimal pretreatment workup is provided and a paragraph is devoted to definitive chemoradiotherapy as an alternative for potentially curative resection. Non-surgical therapies with the aim of palliation are beyond the scope of this thesis.

PART II - STAGING OF OESOPHAGEAL CANCER BASED ON LYMPH NODE INVOLVEMENT

Oesophagectomy for cancer should only be undertaken when a potentially curative R0 resection (complete removal of all – macroscopic - cancer) is expected. It is generally accepted that there is no role for resection in the presence of proven distant metastases (e.g. liver, lung) no matter how localized. This makes preoperative staging of crucial importance. Long-term outcome of oesophageal surgery is strongly stage dependent. For over 50 years the TNM classification has been the standard in classifying the anatomic extent of the disease, reflecting the depth of infiltration (T) and lymphatic (N) and haematogenous (M) spread. In 2010 the latest, 7th edition of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system was presented as the ratification of data-driven recommendations from a worldwide database of thousands of patients with predominantly squamous cell carcinoma. The most important change in this 7th edition of the TNM staging system is that N-stage is defined as the number of involved nodes. Another change in the 7th edition of the TNM staging system is that the concept of non-regional lymph nodes (for example celiac lymph node metastases scored as 'M1' in TNM6) has been abandoned. But although the TNM staging system has been revised from a site-dependent to a numerically based classification, many oesophageal cancer surgeons

have the impression that the location of a positive node is still important, not only for long term survival but also for (pre-)operative planning. In **Chapter 3** a hypothesis-generating study is presented that investigates whether incorporation of information concerning the location of involved nodes besides the number of nodes refines its prediction accuracy, not only based on pathological staging of the surgical specimen but also on clinical staging with preoperative EUS.

It is unknown whether TNM-7 is also generalisable to patients who have undergone a transhiatal approach resulting in pathological specimens with less lymph nodes which potentially impairs the accuracy of staging. Therefore, in **Chapter 4**, the performance of the 7th edition of the TNM staging system for oesophageal cancer is described in a study population of patients with adenocarcinoma who underwent a transhiatal approach.

Besides its potential impact on staging and prognostication that will be addressed in **Chapter 3** and **4**, more extended lymph node retrieval potentially has also a genuine therapeutic impact on survival. However, this has remained a highly controversial issue for decades. The debate has regained attention especially after the broad implementation of neoadjuvant chemoradiotherapy (nCRT). As nCRT is known for its 'sterilising' impact on regional nodes, it is unclear whether extended lymphadenectomy after nCRT is still indicated for prognostic and perhaps even therapeutic reasons. In **Chapter 5** the impact of the neoadjuvant CROSS regimen on the assumed association between the number of removed nodes and survival is investigated.

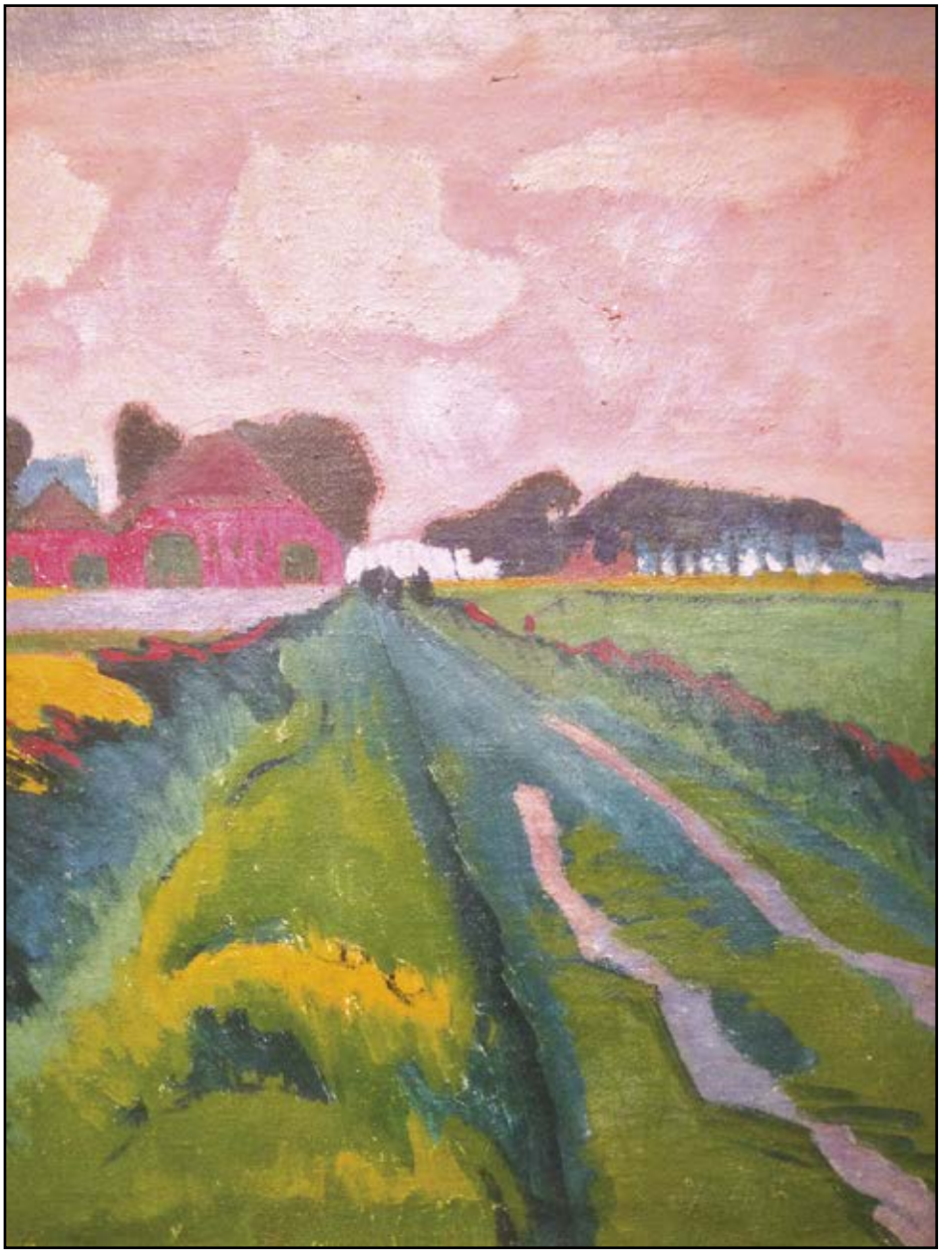
PART III – SURVIVAL AFTER SURGICAL RESECTION OF OESOPHAGEAL CANCER

Surgical resection of oesophageal cancer is still accompanied by a wide variety of complications, inducing substantial morbidity and even mortality. There is an increasing interest in performance indicators because the effectivity of managing these complications varies substantially between institutes. Currently, it is unclear which definition of postoperative mortality best reflects quality of surgical care and how many additional deaths are captured if the time window is expanded after the traditional postoperative period of 30 days. In **Chapter 6** causes of death are described as a function of time after surgery and a proposal is made for the ideal time frame as a proxy for quality of surgical care. Additionally, a case-mix adjustment model is presented for comparison of postoperative mortality after oesophagectomy between institutes.

Many factors have been held responsible for the improved long-term survival that have been achieved over the previous decades, including centralization of care, early tumor detection, improved patient selection based on novel staging modalities, increased use of neoadjuvant therapy, better surgical and anaesthesiological techniques and detailed and standardised perioperative clinical pathways. There is also evidence confirming the influence of surgeon case volume on the outcome of oesophageal surgery. Each of these factors has been investigated separately in relation to survival after oesophagectomy in previous

(sometimes even randomised) studies. The combined implementation of these improvements and their impact on survival on a population-based level are unknown. In **Chapter 7** patient-, tumour- and treatment- characteristics are studied contributing to the previously observed trend of increased survival after oesophagectomy for cancer in the Netherlands. Furthermore, it is analyzed whether the positive impact of multimodality therapy as shown by the randomised CROSS trial can be corroborated on a population-based level.

Future perspectives on oesophageal cancer surgery, staging and survival are given in **Chapter 8** and a summary of the thesis is presented in **Chapter 9**.



Chapter 2

Goals of surgical therapy for esophageal cancer

A.K.TALSMA,
J. SHAPIRO,
B.P.L. WIJNHOVEN,
J.J.B. VAN LANSCHOT

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1. INTRODUCTION

Operative resection of esophageal cancer is probably one of the most challenging procedures in surgery. Partly this is because it encompasses two or even three body compartments: chest and abdomen with or without neck. Moreover, its position immediately adjacent to vital structures (trachea, bronchi, aorta and heart) warrants a careful dissection. With the recent introduction of minimally invasive esophagectomy, the operation has become technically even more demanding. This chapter describes the surgeon's main goals when performing a potentially curative esophagectomy for esophageal cancer, regardless of the surgical approach that is chosen. The various indicators that have been identified to promote oncological control in open surgery will be discussed as well as the tools that help to prevent complications.

In fact, these same goals have to be set for minimally invasive esophagectomy.

2. PRETREATMENT WORK-UP AND STAGING

Multidisciplinary approach

In patients with esophageal cancer a great variety of treatment options are available. For proper medical decision making accurate pretreatment staging is of crucial importance. Early (mucosal) lesions for example can be cured with endoscopic mucosal resection, thus avoiding conventional surgery. At the other end of the clinical spectrum, accurate pretreatment staging is also essential to avoid futile attempts at radical treatment for patients that are in fact incurable due to distant metastases and to guide effective palliation that can be achieved with endoscopic stenting or intraluminal brachytherapy. Discussion of all patients with esophageal malignancies in a multidisciplinary tumor board is recommended because it is associated with improved outcomes after surgery[1, 2]. In a considerable number of patients, the diagnostic work-up or treatment plan is altered after careful evaluation in a multidisciplinary tumor board[3]. Adenocarcinomas arising at the esophago-gastric junction can pose a specific problem for guiding the choice between neoadjuvant chemo- versus chemoradiotherapy and between subtotal esophagectomy versus extended gastrectomy. At present, Siewert type I and II tumors are treated as esophageal cancers while type III tumors are generally treated as gastric cancers.

Patient selection : does the general condition of the patient allow for extensive surgery?

The pretreatment assessment should not only focus on tumor staging but also on optimization of the patient's general condition. The success of a specific treatment modality does not only depend on the tumor-stage, but also on the fitness of the patient. Surgery for esophageal and junctional cancer has a high risk of postoperative (especially pulmonary) complications. Several risk scoring systems have been developed as predictors of poor postoperative outcome. These scoring systems can be used for the individual patient to

guide treatment choice. Moreover, these scoring systems can be used to correct for case-mix differences when comparing performance between hospitals. The prognostic value of the available models however is generally limited. Worldwide, the most widely used and most simple classification is that of the American Society of Anesthesiologists[4], but has been criticized for being subjective. The POSSUM[5] and Charlson score [6] are more comprehensive but are also more cumbersome to calculate[7]. Several series have shown that POSSUM and Oesophageal(O)-POSSUM[8] overestimate postoperative mortality in gastro-esophageal cancer patients[9-11]. The Portsmouth(P)-POSSUM showed less over-estimation and may be the most useful predictor of likely postoperative mortality in these types of patients[12]. Older age (e.g. >80 years) per se is not a contraindication for upper GI surgery, but older patients have increased postoperative mortality and decreased long-term survival after esophageal resection for cancer[13, 14]. Substantial weight loss before surgery was also a negative prognostic factor in several studies [15, 16].

TUMOR SELECTION: CAN THE TUMOR BE RADICALLY RESECTED AND POTENTIALLY CURED?

Over the past decades, long-term survival results have substantially improved. Besides centralization of surgical procedures, early cancer detection, and use of neoadjuvant therapy, improved patient and tumor selection based on novel staging modalities accounts for this improvement[17, 18].

Guidelines for pretreatment staging of patients with esophageal and junctional cancer recommend a number of investigations, including endoscopy with biopsy, endoscopic ultrasonography (EUS), computed tomography (CT) of neck, chest and abdomen, and external ultrasonography (US) of the neck with fine needle aspiration (FNA) of suspected lymph nodes. In addition, positron emission tomography (PET) can also be a useful staging modality, albeit not yet mandatory in e.g. Dutch, UK and USA guidelines. In case of an advanced tumor above the carina bronchoscopy is advised to confirm or exclude invasion of the tracheobronchial tree. Clinical and histopathological staging is generally based on the tumor/node/metastasis (TNM) classification developed by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC)[19]. The most important change in the latest (7th) edition is that the concept of non-regional lymph nodes has been abandoned and that staging of tumors in the esophagus, at the esophogastric junction and in stomach has been harmonized. Number of positive lymph nodes is now more important than their location.

EUS

EUS is superior to any current diagnostic modality for imaging of the primary tumor and its immediate surroundings (T- and N-stage) due to its ability to identify the component layers of the esophageal wall[20, 21]. The main problem with EUS is failure to pass in 1 out of 5

patients[22]. FNA of suspected nodes is only indicated when the results will change the treatment plan (e.g. radiation field). EUS can identify metastatic lymph nodes at the celiac trunk, but is not accurate in detecting distant metastases, with the exception of hematogenous metastases in the left liver lobe and left adrenal gland. FNA of the celiac nodes is technically feasible in 95 % of patients[23].

CT and external US

Spiral CT and external US are used for the detection of distant hematogenous and lymphatic metastases (M-stage). Probably, PET scanning can replace US of the neck, although it is generally recommended to confirm suspected lymph nodes by US-FNA to exclude false-positivity of the PET scan (e.g. due to sarcoidosis)[24]. The ability to accurately predict locoregional resectability is especially important before embarking upon a thoracoscopic or laparoscopic surgical approach to minimize the risk of accidental damage. For this purpose, CT continues to play an important role. Invasion into adjacent organs is unlikely when a periesophageal fat plane can be recognized, but when absent, it cannot be taken as absolute evidence of invasion. This accounts for the overestimation of tumor invasion into trachea, aorta and pericardium.

PET

PET is a non-invasive imaging technique which is increasingly used in the staging of various tumor types, including esophageal cancer[25, 26]. The increased glucose metabolism of malignant cells is the driving force for the uptake of fluorine-18-fluorodeoxyglucose (FDG), which is the most common radiotracer used for oncological PET studies. In addition to qualitative staging (esp. detection of distant metastases), PET is able to quantify FDG-uptake in malignant tissue by calculating the standardized uptake value (SUV) of the primary tumor. After extensive "conventional" diagnostic work-up, additional PET scanning yields a diagnosis of distant dissemination in an additional 10% of patients, especially in case of T3-tumors[27]. The simultaneous, combined PET- and CT-scan is able to localize and classify hotspots more accurately than PET alone.

Intraoperative staging by laparoscopy and sentinel node biopsy

Although inconsistently applied, a systematic review has recommended the use of staging laparoscopy in junctional cancer patients [28], especially for demonstrating low-volume peritoneal disease.

The value of sentinel node (SN) sampling in esophageal cancer is less clear than for e.g. breast cancer and malignant melanoma. In a British study, 96% of SN biopsies accurately detected lymph node metastatic disease[29]. In another study, however, so-called skip lesions were identified in 55% of resected two-field lymphadenectomy specimens[30-32]. Currently, a multicenter trial in Japan is being performed, in which the extent of lymph node dissection during gastric surgery is tailored depending on the SN biopsy[33].

Re-staging

After completion of neoadjuvant therapy patients can be restaged to evaluate response to treatment and to detect any progression of disease before proceeding to surgery. The assessment of nodal disease following chemoradiotherapy by EUS and CT is disappointing because viable tumor cannot be readily distinguished from fibrotic tissue[32, 34]. Studies with PET especially when measuring SUV before and after chemotherapy have been encouraging[35, 36]. Unfortunately, tumor response assessment by PET after neoadjuvant chemoradiotherapy is hampered by radiation-induced inflammation.

Future developments

Recently, more research has focused on staging techniques that address the biological behavior of tumors which is important in the response to chemoradiotherapy and likelihood of recurrence. This can be achieved by PET scanning with novel radiotracers such as (18) F FLT 3-deoxy-3-fluorothymidine or (11)C-choline[37, 38]. Other studies focus on MRI as a potential non-invasive technique for locoregional staging of esophageal cancer[39]. Encouraging results have been achieved in the rapidly improving technology of in vivo intraoperative imaging as well[40].

3. DEFINITIVE CHEMORADIOTHERAPY: AN ALTERNATIVE FOR POTENTIALLY CURATIVE RESECTION?

In recent years two randomized controlled trials compared definitive chemoradiotherapy (dCRT) to neoadjuvant chemoradiotherapy plus surgery (nCRT+S). Both studies employed a non-inferiority design to test the chance that patients in both treatment paradigms have a significantly different survival.

The first study by Stahl et al. [41] included 172 patients between 1994 and 2002 from 11 German centers. It compared dCRT (without salvage surgery) with nCRT+S for 'locally advanced' (i.e. T3-4, N0-1, M0) esophageal squamous cell carcinomas. Two-year survival was 35.4% and 39.9% in the dCRT arm and nCRT+S arm, respectively (P= 0.007). Freedom from local progression was worse in the dCRT arm (40.7% vs. 64.3% respectively; HR 2.1 P=.003). A significant difference was found in treatment related mortality: 3.5% in the dCRT arm and 12.8% in the nCRT+S arm (ǁ 2, P= .03). In summary, there was no difference in overall survival, however local failure was more common, and treatment-related death was less common in the dCRT arm.

The second randomized controlled trial (FFCD 9102) [42] compared dCRT to nCRT+S in patients who had an objective clinical response or an improvement of dysphagia after neoadjuvant chemoradiotherapy (259/444, 58.3%). Two-year survival rates for the dCRT arm and nCRT+S arm were 39.8% and 33.6% respectively (P= 0.03, i.e. the chance that the actual difference is >10%). Three-month mortality (0.8% versus 9.3%, P=0.003) favored the dCRT arm, whereas locoregional relapse (43.0% versus 33.6%, HR 1.63, P= 0.03)

favored the nCRT+S arm.

Both studies suffered from major drawbacks (e.g. inadequate power and lack of standardized chemoradiotherapy protocols), thus precluding more general conclusions from these data. This ambiguity towards dCRT is reflected in clinical practice where in most countries dCRT is reserved only for those patients who are deemed unfit for surgery.

4. SURGICAL PERFORMANCE INDICATORS : ON WHICH PARAMETERS SHOULD MIE BE JUDGED?

Resection margins

The main goal in the surgical treatment for esophageal cancer is the complete removal of the primary tumor and affected lymph nodes. As esophageal cancer easily spreads longitudinally via the submucosal lymphatics, the incidence of intramucosal and submucosal metastases is reportedly high (Figure 1). The completeness of resection of the primary tumor and its intramural metastases can be described with respect to the proximal, distal, and circumferential resection margin and is a well-known determinant of long-term survival in several studies[43-46]. Previous studies have investigated the required length of macroscopic proximal and distal resection margins in order to minimize anastomotic recurrence. A reasonable margin is 10cm for larger tumors and 4 cm for more localized tumors[47]. When only a short proximal resection margin can be obtained through the thoracic exposure (especially for a squamous cell carcinoma) a cervical extension with subtotal esophagectomy is advisable. An adenocarcinoma of the lower esophagus requires an extensive sleeve resection of the lesser curve and fundus to minimize positive distal resection margins.

An esophageal resection can be suboptimal due because of an involved circumferential margin. The definition of circumferential resection margin (CRM) involvement remains controversial. The College of American Pathologists (CAP) and the Royal College of Pathologists (RCP) use different definitions for CRM involvement. Microscopic tumor involvement (R1 resection) is defined by CAP as as tumor found at the cut circumferential resection margin, while it is defined by RCP as any tumor within 1 mm of the circumferential resection plane. Recently, a systematic review was published of fourteen studies involving 2,433 patients. Rates of CRM involvement were 15.3 per cent and 36.5 per cent according to the CAP and RCP criteria respectively. It was shown that CRM involvement is an important predictor of poor prognosis and that the CAP criteria had a greater (negative) prognostic power than the RCP criteria[48]. It can be difficult and time-consuming to identify a positive circumferential resection margin in a large T3 tumor and it has been suggested that this should preferably be done in accordance with the CAP criteria (tumor is found at the inked lateral margin of resection[49]. There has been a significant decrease in CRM involvement especially with the introduction of neoadjuvant chemoradiotherapy[17, 50]. After neoadjuvant chemotherapy CRM involvement still has prognostic importance[51].

Lymphadenectomy

As esophageal cancer readily spreads longitudinally in the submucosal lymphatics, early dissemination to lymph nodes in the chest and abdomen may be involved in cancer of all parts of the esophagus. And even skip metastases, defined as positive distant lymph nodes in combination with negative regional lymph nodes, are encountered relatively frequently[52]. Lymphatic dissemination occurs not only in a chaotic pattern, but also at an early stage. Some 30% of the T1b tumors (with infiltration limited to the submucosa) already have positive lymph nodes involved[53]. Ideally, a complete resection of all locoregional nodes draining the esophagus should include the two or three fields (see above) in addition to the easily accessible periesophageal and perigastric lymph nodes (Figure 2). In a survey among surgeons around the world, the techniqually challenging three-field lymphadenectomy was performed routinely by only 12% of the responders[54]. A SEER analysis showed that the median number of total lymph nodes resected in over 5,600 esophagectomies was only 8 nodes[55]. Lymphadenectomy can be performed safely during minimally invasive surgery and it has been shown that minimally invasive and robotic esophagectomy have similar lymph node retrieval compared to open techniques[56-58].

For staging purposes it is clear that an extended lymphadenectomy is superior to a limited dissection. It has, therefore, been suggested by the 7th edition of the TNM staging system that for staging purposes the total number of resected and identified lymph nodes should be at least 15 nodes. The therapeutic impact of an extended lymphadenectomy is still a matter of debate in esophageal cancer surgery[59]. Some authors state that surgery has reached its limit, while others believe that the course of the disease can be influenced positively by aggressive surgery with an extended lymphadenectomy. One of the hypotheses supporting the benefits of extended lympadenectomy is the clearance of micrometastases that can be present in up to 50% of histology-negative nodes. This hypothesis is supported by the correlation of micrometastases in routine lymph node-negative patients with a poor outcome[60, 61].

More skeptical authors believe that the therapeutic impact of an increased lymph node harvest per se is limited and it is probably not the type of operation performed that makes a difference but rather the stage of the disease at the time of operation[56]. According to this view, lymph node metastases are markers of systemic disease and removal of the primary lesion alone will yield the same survival[62]. The spurious effect of extended lymphadenectomy might then be caused by stage migration which occurs if positive nodes in the extended field change N stage. This results in the so-called 'Will Rogers phenomenon' or 'stage purification' and leads to unreliable stage-by-stage comparisons of survival. For that reason some authors prefer to use the lymph node ratio (i.e. the number of positive nodes over the number of removed nodes) rather than the absolute number of positive nodes[63, 64].

Several prospective trials have been performed comparing survival after esophagectomy with or without extended lymphadenectomy. In the largest RCT (HIVEX-trial), comparing limited transhiatal esophagectomy and extended transthoracic esophagectomy with two-field lymphadenectomy, five-year survival was not significantly different[65, 66]. The survival ben-

efit of an extended lymphadenectomy by a transthoracic approach was limited to a subgroup of patients with low burden of nodal disease (1 to 8 nodes positive on pathological examination of the resection specimen). The identification of this group makes the pretreatment staging very challenging. Unfortunately, unlike in breast cancer, the sentinel node concept has not become popular in esophageal surgery[29, 31]. Several studies have confirmed the higher morbidity after thoracotomy than after transhiatal apporach: more pulmonary complications, more recurrent nerve injuries and higher early mortality [67-69].

Meta-analysis of the available literature data did not show differences in survival between transhiatal and transthoracic operations. Other studies compared fields of dissection, for example the single-center studies by Lerut et al [70] and Altorki et al [71] that suggested a potential survival benefit for three-field lymphadenectomy.

Finally, there are studies that investigated the absolute number of nodes dissected. This has led to different recommendations regarding the optimal extent of lymphadenectomy ranging from 16-30 nodes. In a population of 4,627 patients in the Worldwide Esophageal Cancer Collaboration (WECC), extent of lymphadenectomy was not asscociated with increased survival for patients with extremes of esophageal cancer (TisN0M0 and 7 or more nodes positive and those with well differentiated pN0 cancer[72]. For all other cancers, five-year survival improved with increasing extent of lymphadenectomy. Based on these WECC data a stage-dependent extent of lymphadenectomy was recommended. This is comparable to the findings of the HIVEX trial that showed a better survival after a transthoracic approach in the subgroup of patients with 1-8 nodes positive[66]. Rizk et al identified 18 nodes resected as the minimum necessary for accurate staging and for eliminating an effect of lymphadenectomy on survival[73]. In the study by Altorki et al effect of lymphadenectomy on survival was lost after 25 nodes for early stage and after 16 nodes in stage III and IV cancers[71]. Peyre et al investigated an international database of 2,303 esophagectomies in which survival was maximized with 23 nodes resected[74].

Nowadays, multimodality treatment of esophageal cancer has been widely accepted. As neoadjuvant chemoradiotherapy (CRT) is known to 'sterilize' nodes, it is unclear whether the recommendations for number of lymph nodes from the surgery-alone era still stand. Extended lymphadenectomy seems to be beneficial, particularly in patients who are not down-staged regarding pathological tumor depth (ypT) and those with persistent nodal metastases (ypN+)[75, 76]. The effect of lymphadenectomy is influenced by tumor response after CRT and the survival benefit is stronger in patients without a complete pathological response (non-pCR) compared to those with pCR[77].

Morbidity – Prevention of complications

The typical esophageal cancer patient suffers from several co-morbidities including obesity (especially in adenocarcinoma) and cardiopulmonary diseases (in both squamous and adenocarcinoma) that put the patient at increased risk for postoperative complications. Serious intraoperative and postoperative complications can occur with minimally invasive as well as open techniques, also depending on the need of a thoracic phase of the operation. Overall,

complication rates are reported in over 50% of esophagectomy series, with incidence varying between 17 and 74%[78, 79]. Postoperative complications have been directly linked to a variety of other outcome parameters including mortality, readmission rate, early cancer recurrence, survival, length of hospital stay, costs and resource utilization and quality of life[80-83]. The most important issues in the management of perioperative complications are prevention and early detection. However, a clear understanding of the relationships between complications, their recognition, management and how they influence subsequent mortality, is hampered by the lack of standardized definitions [84, 85]. Finally, early detection and proper management of postoperative complications is of crucial importance. It has been shown repeatedly that the so-called "failure to rescue" largely explains the difference in mortality rates between low-volume and high-volume hospitals for complicated surgery including esophagectomy[86].

The exact role for minimally invasive techniques is still not fully clear. The increased magnification offered by thoracoscopy might decrease complications, but lack of tactile control is probably a contributory factor to the increase of intraoperative injuries. It is unlikely that minimally invasive methods will reduce mortality rates since in experienced centers death after open esophagectomy is already a rare event. Minimally invasive esophagectomy (MIE) might be proven superior for other endpoints such as blood loss, duration of ICU or hospital stay, need for analgesics and pulmonary function. The best available evidence comes from a recently published RCT (TIME-trial) showing that MIE is accompanied by less pulmonary complications[87]. This trial has been criticized because of the lack of a clear definition of "pulmonary complications" as the primary endpoint[88]. Moreover, an unexplained increase of recurrent nerve injuries was present in the open group.

Respiratory complications

Respiratory failure is a major problem after esophagectomy. Several studies have reported that about half of the in-hospital deaths after esophagectomy is due to pneumonia, which is the most frequent general complication after surgery[89]. Preventive measures include preoperative respiratory training, cessation of smoking and continuous postoperative pain control by epidural analgesia in order to avoid restrictive respiration and insufficient coughing. Micro-aspiration as a consequence of impaired swallowing coordination because of a cervical anastomosis also plays a role in the pathophysiology of bronchopneumonias. Another reason for postoperative respiratory impairment is a large pleural effusion, which should be drained if provoking extended atelectasis. Avoiding the need for a combined thoracotomy and laparotomy may potentially reduce postoperative pain, ventilator dependence and cardiopulmonary complications[90]. In a study comparing thoracoscopic resection with a historical cohort the overall incidence of pulmonary complications was reduced from 33% to 20%[91]. Probably cardiopulmonary complications do not depend on the incision size only. The benefit of smaller port sites that are needed during minimally invasive surgery may be offset by the lengthened time of operation and single-lung ventilation.

Recurrent laryngeal nerve injury

More recurrent laryngeal nerve injuries when using thoracoscopy have been reported, which might be attributed to the use of diathermia. Others claim that the use of minimally invasive techniques has lowered the incidence of hoarseness because of the magnified view[87].

Anastomotic leakage

Lack of standardization of definitions is a problem when reporting on complications. In a recent meta-analysis anastomotic leakage was reported in most of the publications, but it was defined in only a minority with 22 differing definitions [84]. Early disruption of the esophagogastric anastomosis is the result of a technical problem and immediate re-exploration is frequently indicated for correction. Many different suturing and (semi-) mechanical techniques have been described. The semimechanical side-by-side technique claims a lower leakage rate compared to a hand-sewn anastomosis, but has not been tested in a randomized trial[92, 93]. Leakage is more frequent in the neck than in the chest, but the associated mortality might be lower, especially after a transhiatal approach[94]. If a transmural necrosis of the gastric conduit is suspected, this can be diagnosed by endoscopy and when present is also an indication for surgery with formation of a cervical esophagostomy, resection of the gastric tube and placement of a feeding jejunostomy. After rehabilitation of the patient, a colonic interposition can be performed at a secondary stage. Late disruptions become manifest generally between postoperative day 5 and 10 and are most frequently due to ischemia. They can be managed non-operatively in most cases with aggressive drainage using radiologically guided drains or endoluminal vaccum therapy[95]. Self-expandable stents can be inserted in these situations but can have the disadvantage of migration or further necrosis due to tissue compression ultimately leading to e.g. neoesophago-tracheal fistula formation.

Chylothorax

The incidence of accidental thoracic duct leakage can be diminished by intraoperative identification and ligation of the duct. Reported incidence of chylothorax varies between 3% and 10% and is seen more often in patients who undergo transthoracic esophagectomy and in patients who have more positive nodes. Patients with chyle leakage have more pulmonary complications. Conservative therapy (initial parenteral feeding and subsequent enteral diet with medium-chain triglycerides (MCT)) is often successful, but operative therapy should be seriously considered in patients with a persistently high daily output of more than 2 L after 2 days of optimal conservative therapy[96].

Cardiac arythmias

Cardiac arhythmias are not uncommon in the postoperative phase. Atrial fibrillation (AF) is seen in 15-20% of patients and requires further investigation because it can be an early manifestation of e.g. mediastinitis due to intra-thoracic anastomotic leakage. AF can also be associated with hypervolemia, pre-existent pulmonary or cardiac disease and dilation of the gastric conduit.

MORTALITY AND QUALITY CONTROL

Definitions

There is an increasing interest in comparing institutional performance. For surgical procedures postoperative mortality rate is generally used, because it is a relatively objective measure and reflects the summation of the most severe postoperative complications. Currently it is unclear which definition of postoperative mortality best reflects surgical quality of care. The 30-day operative mortality (30DM) and the in-hospital mortality (IHM) after esophageal resection are well documented and vary from 4% for specialized centers to > 10% for nationwide registries[97]. Few studies report on mortality beyond 30 days. Damhuis et al. however showed in the Dutch Cancer Registry that 43% of in-hospital deaths after surgery for esophageal cancer occurred 30 days or more after the operation[98]. Therefore, 90-day mortality (90DM) might be preferred as a performance indicator. Using a longer time period after the operation for defining postoperative mortality may thus provide a better definition of quality of surgery[99]. Extending the mortality period beyond 30 days and beyond in-hospital stay has the advantage that patients who die because of surgery related complications outside the hospital are included as well.

Not only short-term outcomes, but also long-term survival should be part of the benchmark as both aspects are relevant for comparing surgical performance. Both surgery-related deaths and cancer recurrence related deaths are reflections of surgical quality of care. Less radical surgical resections will generally result in lower postoperative morbidity and mortality, but will generally give less favorable oncological outcomes.

Case mix correction

Even after agreement on a uniform definition of postoperative mortality, direct comparison of crude mortality rates between hospitals can be misleading as they do not take into account the case-mix difference, i.e. the differences in physiological condition and tumor stages of patients. Sophisticated models have been developed for prediction of 30DM and IHM [8, 14, 67, 100-104] after esophageal surgery, but models for 90DM have been mostly based on large multi-institutional databases with only few parameters available[105].

Outcome-volume relationship and registration

Over the past decades, better long-term survival results have been presented, evolving from 18 % 5-year survival in the era from 1980-1990 to 48% in the most recently published RCT (Table 1) [17, 65, 99, 106, 107]. It is suggested that many factors are responsible for this positive effect, including large hospital volume, early tumor detection, improved patient selection based on novel staging modalities, increased use of neoadjuvant therapy, better surgical and anesthesiological techniques and improved standardized perioperative clinical pathways[18, 108]. In many countries around the world it has been decided that high-risk surgical procedures such as esophagectomy should be restricted to facilities with a yearly minimum volume [109, 110]. It has been demonstrated that the incidence of postoperative

complications is similar across hospitals but that the associated mortality rates are lowest in high volume centers, which generally show a lower “failure to rescue” [86, 111]. Centralization is currently implemented widely. Also auditing has been implemented as a way of improvement of care. Of course this results in an additional registration burden for the surgeon, but comparing individual or institutional results with the benchmark has proven valuable in other types of cancer surgery, such as for rectal cancer[112] [113]. For esophageal cancer, variables of interest are for example hospital mortality, radicality (R-status), extent of lymph node dissection, length of hospital stay, application of neoadjuvant therapy, availability of PET-CT and the presence of a well-structured MDT. The quality indicators can be divided in structural, process and outcome measures respectively (Table 2) [114]. Heterogeneity and lack of standardized definitions of the outcome of interest is a problem here as well. In a review of esophagectomy outcomes from 164 NSQIP (National Surgical Quality Improvement Project) hospitals it was demonstrated that even following case mix adjustment, results between centers varied by 161 % for 30-day mortality and 84% for serious morbidity[67]. Finally, comparing the quality of infrequent operations such as esophagectomies is difficult, besides issues of definition and case-mix correction, because of another complex element in comparing surgical performance, i.e the problem of sample size [115].

CONCLUSION / TAKE HOME MESSAGES

- Discussion of all patients with esophageal malignancies in a multidisciplinary tumor board is recommended and is associated with improved outcomes after surgery.
- ASA, (O-)POSSUM and Charlson are the preoperative risk scoring systems that are often used in esophageal surgery.
- The most important change in the most recent 7th edition of the TNM staging system is that the concept of non-regional lymph nodes has been abandoned and that staging of esophageal cancer has been harmonized with gastric cancer.
- After extensive "conventional" diagnostic work-up, additional PET scanning yields a diagnosis of distant dissemination in an additional 10% of patients, especially in case of T3-tumors.
- The goals that have been achieved in open esophageal surgery should also act as targets for minimally invasive esophagectomy, being a lymph node retrieval of at least 15 nodes, R0 resection (>1mm margin) and operative mortality < 5%.
- Neoadjuvant chemoradiotherapy decreases the incidence of a tumor-positive circumferential margin.
- Meta-analysis of the available literature data did not show differences in survival between transhiatal and transthoracic operations. The survival benefit of an extended lymphadenectomy by a transthoracic approach seems to be limited to a subgroup of patients with low burden of nodal disease.
- Overall, complication rates are reported in over 50% of esophagectomy series, with incidences varying between 17 and 74%. Postoperative complications have been directly linked to a variety of other outcome parameters including mortality, readmission rate, early cancer recurrence, survival, length of hospital stay, resource utilization and quality of life.
- It has been suggested that MIE is accompanied by less pulmonary complications.
- The 30-day operative mortality (30DM) and the in-hospital mortality (IHM) after esophageal resection vary from 4% for specialized centers to > 10% for nationwide registries.
- Many factors are responsible for the better long-term survival rates that have been achieved over the previous decades, including large hospital volume, early tumor detection, improved patient selection based on novel staging modalities, increased use of neoadjuvant therapy, better surgical and anesthesiological techniques and improved standardized perioperative clinical pathways.
- The lack of standardized definitions of complications and mortality has hampered outcome assessment after open and minimally invasive esophagectomy

Table 1
Several studies over previous decades showing improved long-term survival after esophageal resection.

Study	Randomization	Survival
Muller, 1990[106]	N/A	5-y survival 10 %
Walsh, 1996 [107]	Multimodality therapy vs surgery	3-y survival 32 %
Hulscher 2002, Omloo 2007 [65, 66]	Transthoracic vs transhiatal approach	5-y survival 36 %
Van Hagen, 2013 [17]	Multimodality therapy vs surgery	5-y survival 47%

Table 2
Performance indicators that have been identified in esophageal cancer surgery[114]

Quality-of-care indicators
Structural measures
Hospital volume
Surgeon volume
Centralization
Process measures
Discussion in Multidisciplinary Board
Age
Pre-operative quality of life
Staging (FDG-PET versus FDG-PET)
Lymphadenectomy
Neoadjuvant chemoradiation
Surgical approach
Outcome measures
Postoperative complications
Radicality of resection
Number of resected lymph nodes

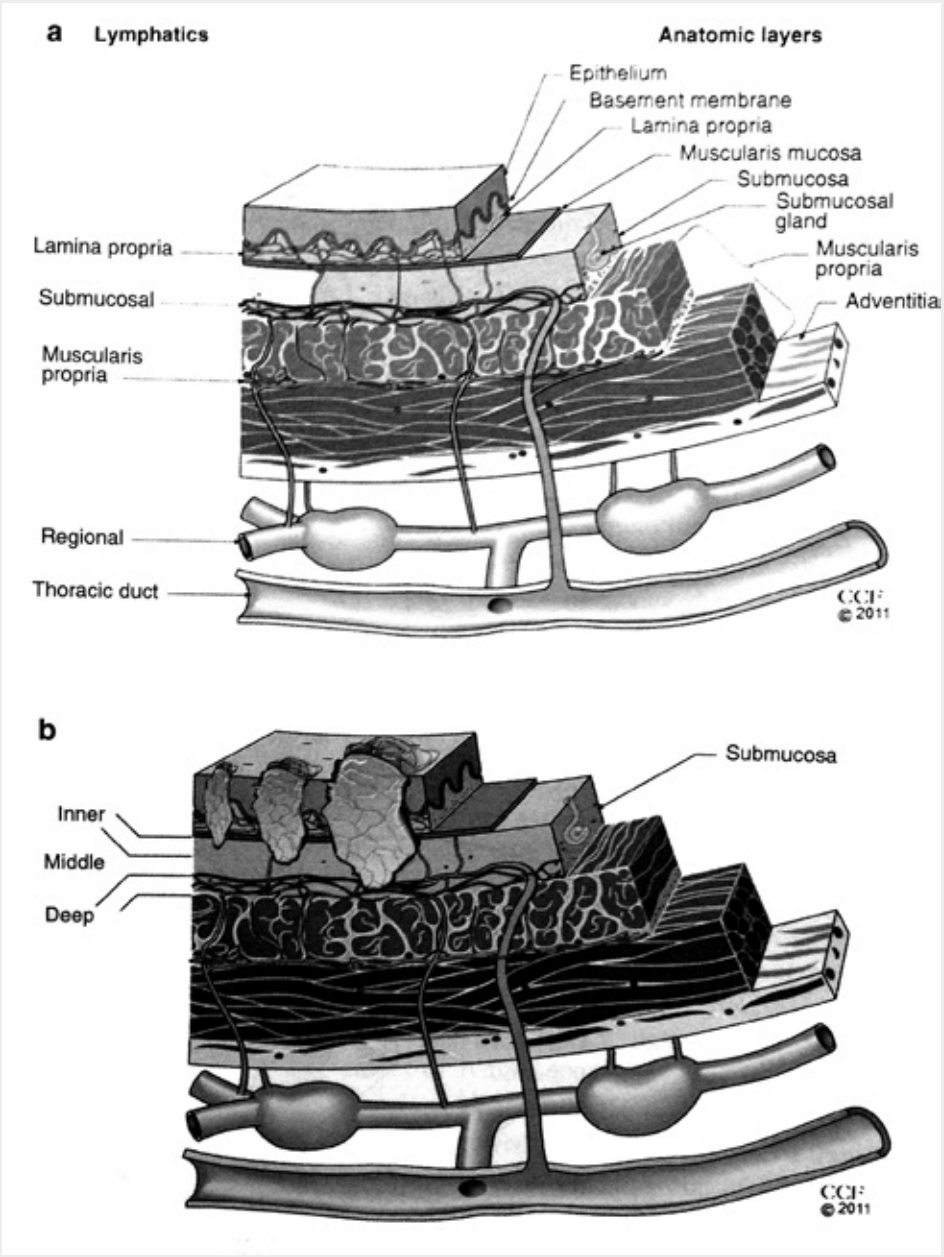

Figure 1
The lymphatics of the esophagus are distributed in the form of a submucosal and a paraesophageal plexus that can both drain directly into the periesophageal lymph nodes (copyright Elsevier; Siva Raja et al. Esophageal submucosa: The watershed for esophageal cancer The Journal of Thoracic and Cardiovascular Surgery 2011. 142(6):1403-11).

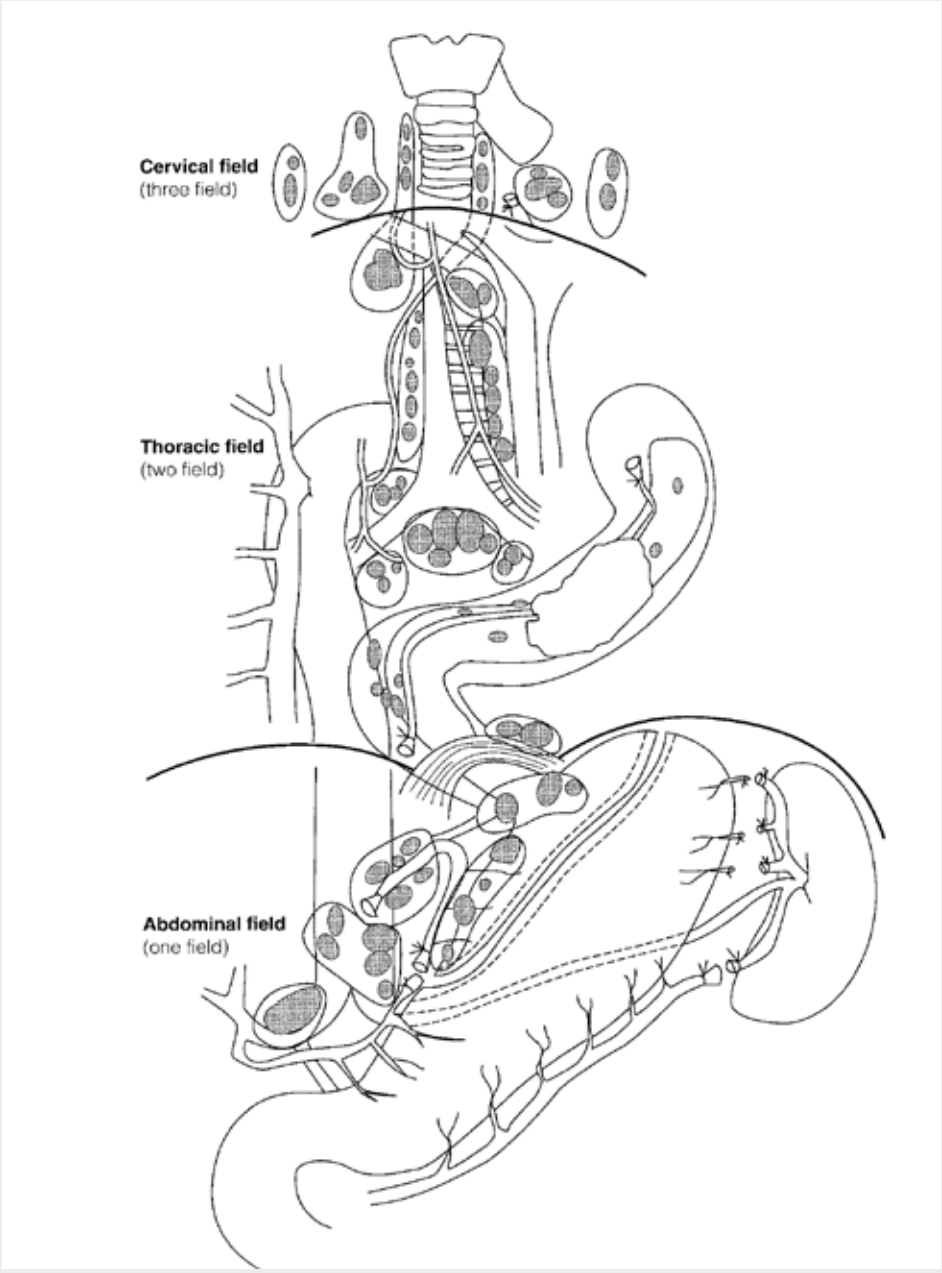

Figure 2
Extent of resection and fields of lymph node dissection routinely carried out for cancer of the esophagus (previously published in Griffin S., Raimes SA. A companion to specialist surgical practice : oesophagogastric surgery 4th ed. Elsevier ; 2009:97).

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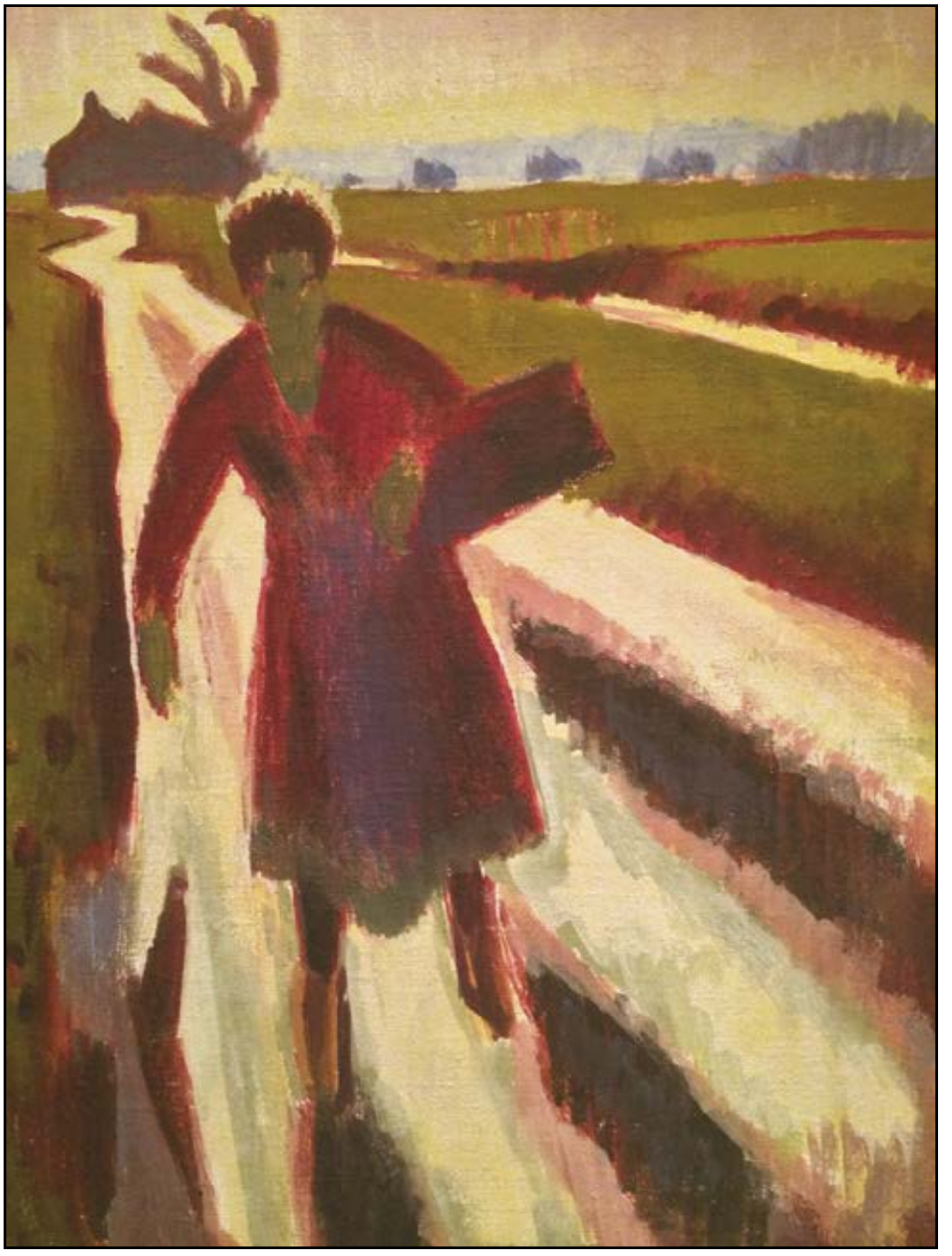

Chapter 3

Location of lymph node involvement in patients with esophageal adenocarcinoma predicts survival

AALDERT K. TALSMA[1], MD MSC,
CHIN-ANN J. ONG[2], MD,
XINXUE LIU[2], PHD,
PIETER VAN HAGEN[1], MD,
JAN J.B. VAN LANSCHOT[1], MD PHD,
HUUG W.TILANUS, MD PHD[1],
RICHARD H. HARDWICK[3], MD FRCS,
NICHOLAS R. CARROLL, MD[3],
MANON C.W.SPAANDER[4], MD PHD,
REBECCA C. FITZGERALD[2], MD MB BCHIR,
BAS P.L.WIJNHOVEN[1], MD PHD

1 Department of Surgery and Gastroenterology[4],
Erasmus Medical Center, Rotterdam, The Netherlands
2 Medical Research Council (MRC) Cancer Cell Unit,
Hutchinson/MRC Research Center, Cambridge, UK
3 Cambridge Oesophago-gastric Center,
Addenbrookes Hospital, Cambridge, UK

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ABSTRACT

Background

Location of positive lymph nodes has been abandoned in the 7th classification of the TNM-staging system for esophageal adenocarcinoma. The present study evaluates whether distribution of involved nodes relative to the diaphragm in addition to TNM 7 further refines prediction.

Methods

Pathology reports of patients who underwent esophagectomy between 2000 and 2008 for adenocarcinoma of the esophagus were reviewed and staging was performed according to the 7th UICC-AJCC staging system. In addition, lymph node involvement of nodal stations above and below the diaphragm was investigated by endoscopic ultrasonography (EUS) in a separate cohort of patients who were scheduled for esophagectomy between 2008 and 2009 at two institutions. Survival was calculated by the Kaplan-Meier method, and multivariate analysis was performed with a Cox-regression model.

Results

Some 327 patients after esophagectomy for cancer were included. Multivariate analysis revealed that patients with 3-6 involved lymph nodes in the resection specimen on both sides of the diaphragm had a twofold higher chance of dying compared to patients with the same number of lymph nodes on one side of the diaphragm.

EUS assessment of lymph node metastases relative to diaphragm in 102 patient showed that nodal involvement at both sides of the diaphragm was associated with worse survival as compared to patients with nodes on one side or no involved nodes (HR and 95%CI:2.38[1.15-4.90]).

Conclusions

A combined staging system that incorporates distribution of lymph nodes relative to the diaphragm refines prognostication after esophagectomy as assessed in the resection specimen and pre-treatment as assessed by EUS. This improved staging has potentially a great impact on clinical decision making as to whether to embark upon potentially curative or palliative treatments.

INTRODUCTION

Surgery with neoadjuvant chemo(radio)therapy for resectable esophageal cancer offers the best chance for long term survival [1]. Following esophagectomy, prognosis is largely determined by the depth of infiltration of the primary tumor and the lymphatic or hematogenous spread, traditionally reflected in the histopathological TNM classification [2]. Lymphatic dissemination in adenocarcinomas of the distal esophagus and gastro-esophageal junction is frequenty seen in the lymph nodes located in the middle-lower mediastinum and in the upper abdomen around the celiac axis.

Driven by several large retrospective studies, the 7th edition of the UICC-AJCC esophageal TNM staging system (TNM 7) has acknowledged the prognostic importance of the number of involved nodes on survival by subdividing the N-classification into N0-N3 [3]. However, this system does not take into account the location of involved nodes. Peters et al. [4] have demonstrated that a revised N-classification that incorporates both burden and distribution of involved nodes relative to the diaphragm provided improved prognostic power. It is unclear whether location of positive lymph nodes in relation to the diaphragm can refine the latest TNM-staging system for esophageal cancer patients.

Although histopathological staging does reflect patient's prognosis after esophagectomy, accurate pre-treatment clinical staging is important for deciding whether to embark upon potentially curative or palliative treatment and for informing patients about their prognosis. Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has the highest accuracy for the assessment of the T- and N-stage [5]. However, clinicians struggle to put EUS findings into clinical practice as TNM 7 has abandoned M1a metastases. Also assessment of the number of involved nodes using EUS in a busy clinical practice is time consuming, difficult and inaccurate [6]. In contrast, determination of the 'bulk' of nodal involvement relative to the diaphragm regardless of the exact number of involved nodes might be a more easily adopted and clinically useful approach.

The first aim of the study was to evaluate if number and distribution of involved lymph nodes relative to the diaphragm, as determined in the resection specimen, can accurately prognosticate patients with esophageal adenocarcinoma. The second aim was to assess if preoperative EUS staging of lymph node distribution relative to the diaphragm can predict prognosis of patients.

METHODS

To address the first study objective, patients who underwent esophagectomy with curative intent between January 2000 and September 2008 at the Erasmus University Medical Center Rotterdam, the Netherlands, for adenocarcinoma of the esophagus or esophago-gastric junction (EGJ; Siewert type 1 and 2) were identified from a prospective database. All patients underwent the standard diagnostic work-up including endoscopic ultra-

sound (EUS), CT-scan of chest and abdomen and ultrasonography of the neck. A PET scan was not routinely performed during the study period. Some patients received neoadjuvant chemo(radio)therapy in the context of randomized controlled trials [7,8]. Induction chemo-radio- or chemotherapy was given to patients with either a cT4-tumor without distant metastases or in patients with gross involvement of celiac trunk lymph nodes who were not considered candidates for primary surgical therapy. Pathology reports were reviewed and pN-stage was scored according to TNM 7. The sites of lymph nodes were classified according to the nomenclature and code number of the Japanese Society for Esophageal Diseases [9]. Patients were further classified as having involved nodes on one side or on both sides of the diaphragm. Lymph node metastases designated in the report as 'peri-esophageal', 'subcarinal', 'paratracheal' or 'aortopulmonary window' were considered to be above the diaphragm whereas 'perigastric', 'paracardiac', 'left gastric artery', 'splenic artery', 'common hepatic artery' or 'celiac trunk' nodes were considered as being below the diaphragm. In particular, the subcarinal, paratracheal, aortopulmonary, celiac trunk, left gastric, splenic artery and common hepatic artery lymph node stations were mainly designated by the surgeons during surgery and placed in separate containers. The nodal stations which can be identified anatomically from the specimen (peri-esophageal, perigastric and paracardiac) were present with the specimen en-bloc and were removed by the pathologist. When the pathologist identified nodes that could have been sterilized in patients who received neoadjuvant therapy, these were counted as negative.

To evaluate the prognostic value of EUS in detecting nodes above and below the diaphragm, consecutive patients who were scheduled for an esophagectomy for adenocarcinoma of the esophagus or EGJ at the Erasmus MC or Addenbrooke's Hospital (Cambridge, UK) between 2008 and 2009 were identified. Experienced endoscopists performing the EUS were specifically prompted by the study team to look for the relationship of involved lymph node stations with the diaphragm (cN-stage) and to include this into the formal report since 2008. On EUS a lymph node was considered malignant based on morphological criteria [10]. FNA sampling was not so much driven by these criteria but rather by the presence of suspected nodes outside the surgical and radiation field which positivity would change the treatment plan. In case FNA of lymph nodes was performed, the initial endoscopic classification was not changed when the cytology results were disclosed.

Surgery

Transhiatal esophagectomy encompassed the en bloc dissection of the distal esophagus and its adjacent lymph nodes under direct vision through the widened hiatus of the diaphragm up to the level of the inferior pulmonary vein. The paracardial, lesser curvature, left gastric artery, celiac trunk, common hepatic artery, and splenic artery nodes were dissected and a gastric tube was created. After mobilization and transection of the cervical esophagus, the intrathoracic part was bluntly dissected in an antegrade fashion with a vein stripper. Esophagogastrostomy was performed in the neck. The left gastric artery was marked in the operation specimen with a suture.

In Rotterdam, a transthoracic esophagectomy was mainly done during the study period in the context of a randomized controlled trial [11]. The thoracic duct, azygos vein, ipsilateral pleura, and all peri-esophageal tissue in the posterior mediastinum were dissected en bloc via a right-sided thoracotomy. The resection specimen included the lower and middle mediastinal, subcarinal, and right-sided paratracheal lymph nodes, that were collected as separate samples as well as nodes in the aortopulmonary window. The abdominal and cervical phase of the transthoracic procedure were identical to the transhiatal procedure.

Follow-up

Surviving patients were followed at regular intervals at the outpatient clinic until five years after the operation. Overall survival was defined as the time between date of operation and date of death. Surviving patients were censored on the day of last follow-up. Patient survival status was calculated after contacting the general practitioners or the municipal mortality registers by a trained data manager. Last follow-up checkpoint was July 31st 2011.

Statistical Analysis

Univariable and multivariable Cox regression analyses were performed to assess the associations between overall survival and histopathological and clinical lymph node staging systems. Hazard ratios were reported for each variable analyzed. Overall survival rates were estimated by the method of Kaplan–Meier and log rank test was used to determine statistical significance. Two-tailed $P<0.05$ was considered statistically significant. All the analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Importance of lymph node number and location

From the database 392 patients were identified. Two patients were excluded because of missing information on the number of positive lymph nodes and date of last follow up. In addition, 63 patients with squamous cell cancers were excluded. The clinical characteristics and univariate analysis of the 327 patients are shown in Table 1. The overall 5-year survival rate was 34.6%. Overall survival according to TNM 7 is shown in Figure 1A. Patients with involved lymph node metastases on both sides of the diaphragm had a significantly poorer survival as compared to patients with nodal disease on one side of the diaphragm or N0 disease ($p<0.001$; Figure 1B).

Adjusting for all significant variables from the univariable analysis, multivariable analysis showed that nodal involvement on both sides of the diaphragm is associated with a higher hazard for death as compared to nodal involvement on one side of the diaphragm. Analysis of the number of lymph nodes sampled in each group showed that there was no difference in the number of lymph nodes sampled which could account for the prognostic effect observed (Supplementary figure 1). Location of the primary tumor did not have impact on

prognostic significance of positive lymph nodes found above and below the diaphragm. In addition, subset analysis performed on patients who underwent transhiatal resection (n=313) or did not receive neoadjuvant chemoradiotherapy (n=220) consistently showed that involvement of lymph nodes of both sides of the diaphragm was a significant prognostic factor (Supplementary Table 1). Lastly, in view that location of nodal involvement should be combined with current staging criteria with the possibility of N3 status (>6 involved lymph nodes), we performed a subset analysis on patients with at least 7 lymph nodes sampled. Patients with nodal involvement on both side had the highest hazard ration of death (2.88; 95% CI:1.68-4.94; supplementary Table 1). Combining the nodal categories as dictated by TNM 7 with the location relative to the diaphragm in a Cox regression analysis model resulted in the hazard ratios for each group, as summarized in Table 2. Notably, after adjusting for covariates, patients with 3 to 6 involved lymph nodes distributed on both sides of the diaphragm had a markedly increased risk of death (HR=2.93;95%CI:1.79-4.79) as compared to patients with 3-6 involved lymph nodes that resided on one side of the diaphragm (1.74; 95%CI:0.94-3.21).

From the finding in the Cox regression analysis that location only affects prognosis in the group of patients with 3-6 lymph nodes involved (N2), two survival curves for N2 were calculated and drawn in Figure 1C. Patients with 3 to 6 involved lymph nodes on one side of the diaphragm have a similar prognosis (5-year survival rate 29.7%) when compared to patients with 1-2 involved lymph nodes (5-year survival rate 27.0%) while the 5-year survival rate is 10.4% for patients with 3-6 involved nodes on both sides of the diaphragm.

Prediction of survival with EUS

One hundred and twenty two patients (55 from Rotterdam and 67 from Cambridge) underwent pretreatment EUS for esophageal adenocarcinoma between 2008 and 2009 to determine the number and location of involved lymph nodes. Patients with missing information on EUS location, because the endoscope could not pass the tumor (n=14), incomplete follow-up (n=1) or who were irresectable intraoperatively (n=5) were excluded, leaving 102 patients for analysis.

Lymph node metastases were detected by EUS in 66.7% of patients. Positive lymph nodes on both sides of the diaphragm were seen in 15.7 % of patients. Patients with suspected lymph nodes on both sides of the diaphragm had a significantly worse overall survival as compared to patients with nodal disease on one side of the diaphragm or with no positive lymph nodes identified at all (cN0) with 2-year survival rates of 34.7 % and 61.1% respectively (p = 0.027; Figure 2).

After adjusting for age, sex, chemoradiotherapy and study center, patients with node positivity on both sides of the diaphragm had a higher risk of death as compared to patients without node positivity on EUS (Table 3). However, no significant difference was found between patients with one-sided nodal disease and those without node positivity. With the latter two categories combined, a statistically significant difference was found when compared to patients with positive nodes on both sides of the diaphragm (HR and 95%CI: 2.38[1.15-4.90]).

DISCUSSION

Surgical resection margin, depth of tumor invasion and lymph node status are the most important predictors of outcome in patients with esophageal cancer. The lymphatic drainage pattern of the esophagus is complex with abundant lymph-capillary networks especially in the submucosa [12]. This results in a longitudinal lymphatic drainage as opposed to segmental drainage as is the case in colorectal cancer [13]. Lymphoscintigraphy indicates that the main lymphatic pathways originating from the distal esophagus preferentially drain into the lymph node stations in the upper abdomen but also upwards into the mediastinum [14]. From previous studies we know that intra-thoracic lymph node metastases in patients with cardiac tumors are associated with a poor prognosis [15-18].

Identification of patients who will not benefit from surgical therapy is an important issue. Despite a great need for accurate staging prior to treatment of esophageal cancer, proposed modifications of TNM staging are mostly based on post-surgery pathological staging. Moreover, location of positive lymph nodes has been abandoned in the 7th classification of the TNM. The present study shows that besides the number also the distribution of involved lymph nodes in relation to the diaphragm refines prediction of prognosis. A combined lymph node staging system is proposed in which patients currently staged as N2 (3 to 6 lymph nodes involved) comprises 2 groups of patients that can be distinguished by the distribution of the involved lymph nodes relative to the diaphragm. Multivariable analysis demonstrated that N2 disease distributed at both sides of the diaphragm was associated with a worse outcome compared to patients with the same number of lymph nodes involved but one side of the diaphragm. Subgroup analysis showed the same prognostic effect of lymph node metastases located at both sides of the diaphragam after stratification for location of primary tumor in the distal esophagus versus a tumour located at the gastroesophageal junction. In addition, after adjusting for number of positive lymph nodes and other covariates in our cohort, nodal involvement on both sides of the diaphragm still confers a poorer prognosis than nodal involvement on one side of the diaphragm. It should be noted that the determination of location of nodal involvement on esophagectomy samples requires careful coordination between the surgical and pathological services. In our experience, nodal stations that cannot be identified from anatomical landmarks of the specimen (eg subcarinal) should be identified as separate stations by the surgeon whereas nodal stations resected en-bloc with the stomach can easily identified by the pathologist.

More importantly, we have demonstrated that, before surgery, assessment of location by EUS was able to identify a subset of patients at high risk for early death. This study shows that EUS is useful in dichotomizing patients' preoperative nodal stage into locoregionally early (one-sided disease) or advanced (both-sided disease), which is very hard to do by counting individual nodes. It is the adequate pre-operative assessment of clinical TNM stage that largely determines whether a patient will benefits from surgery at all or whether surgery will not cure the disease [19,20]. Other studies have examined the value of EUS as a predictor of long-term survival in esophageal cancer patients [21-24] but no

study has examined the prognostic significance of the location of lymph node metastases on ultrasonography before.

A surprising finding was that location of involved lymph nodes was able to predict survival during clinical staging by EUS, but lost its statistical significance after surgery in the assessment of the resection specimen. An explanation could be that post surgery effect of nodal status was diluted by stage migration secondary to neoadjuvant therapy with involved lymph nodes sterilized in the final surgical specimen. Sensitivity analysis in which patients who underwent neoadjuvant treatment were excluded did not change the hazard ratios in multivariable analysis and hence neoadjuvant therapy did not introduce selection bias.

The present study has limitations. Because the overall accuracy for EUS in predicting the N-stage per nodal station is moderate, mainly because of a high false-negative rate, this might give rise to an underestimation of the number of patients with nodal involvement on both sides of the diaphragm. In the absence of FNA, accuracy is 80% [25]. In an earlier study from Rotterdam, EUS predicted nodal status correctly in 137 out of 202 lymph node stations[6]. The accuracy was better for those stations located high in the chest (paratracheal and aortopulmonary window nodes) than for the peritumoral lymph nodes (subcarinal, paraesophageal and lesser curvature nodes). The lack of FNA sampling is not so much an issue in this paper that considers prognostication before surgery. If a lymph node would have been proved positive at a defined metastatic site, there would be no need to prognosticate anymore as the patient would go down the palliative pathway. Moreover, FNA adds considerable time to EUS and in the real world is often not done routinely. So the lack of FNA could also be considered a strength of the study and the results are likely to be external valid.

Secondly, transhiatal esophagectomy, which was the predominant surgical approach in this study, may have affected the completeness of mediastinal lymph node dissection. How extensive a lymph node dissection should be for proper staging is unknown. In the present study a transhiatal approach was associated with a better outcome. This is probably a biased effect due to 'confounding by indication': patients clinically staged as having more advanced disease were more often offered a transthoracic approach. A transthoracic approach yields more lymph nodes and thus a more robust nodal staging. It should therefore be noted that in the present study there is a risk of understaging - especially for lymph nodes above the diaphragm – and hence underestimation of the shown effect. We don't feel that distribution of lymph nodes relative to the diaphragm is a surrogate of the number of nodes involved. Indeed there is a mean difference of 0.85 lymph node (4.39 positive lymph nodes in "3-6 LN both sides group" versus 3.54 positive lymph nodes in "3-6 LN one side group"; data not shown) but this difference is too small to explain the effect. Moreover, both mean number of nodes would be categorized as N2 by the 7th edition of the TNM staging system and apparently distribution relative to the diaphragm further stratifies prognosis.

Thirdly, the determination of nodal location following resection was left up to the pathologists. It is the experience of many surgeons that especially nodes around the esophago-

gastric junction will be difficult to accurately localize unless the pathologist is directed by immediate feedback from the operating surgeon.

Fourth, the EUS examinations were all performed by experienced endosonographers. While this may be considered a relative strength of the study, it may also be a potential weakness, because the results may not be applicable to centers with lower case loads, or without expert endosonographers.

Finally, during the study period, only thirty-five percent of patients underwent neoadjuvant therapy. This number is different from current Dutch and worldwide practice and might influence generalizability to the worldwide population of patients with esophageal adenocarcinoma.

In conclusion, this retrospective study supports a subclassification of N-stage based on both number and location of lymph node metastases relative to the diaphragm, from both a clinical and a histopathological perspective. Because of the retrospective design and its intrinsic limitations, the study is only hypothesis generating. It supports the feeling of many surgeons that survival is related not only to the number of nodes involved, but also their anatomical location. It has to be validated whether a 'hybrid' staging system that is similar to TNM 7, but incorporates both number and location of involved lymph nodes, still stands using promising staging modalities such as contrast enhanced EUS or MRI with different types of contrast [26], preferably in association with CT (FDG) PET imaging.

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Table 1
Clinico-pathological characteristics and univariate analysis of 327 patients who underwent resection for esophageal adenocarcinoma*

		HR	p-value
Age (yrs)	62.9 (10.4)	1.03 (1.01-1.04)	<0.01
Follow up (yrs)			
All patients	2.2 (0 - 10.3)		
Surviving patients	5.9 (2.1 – 10.3)		
Gender			
Male	286 (87.5)	Reference	
Female	41 (12.5)	0.80 (0.52-1.22)	0.31
Tumor category (pathology)			
T0	9 (2.8)	0.68 (0.21-2.24)	0.53
T1	61 (18.7)	Reference	
T2	57 (17.4)	1.03 (0.60-1.76)	0.93
T3	199 (60.9)	2.94 (1.97-4.41)	<0.01
T4	1 (0.3)	19.75 (2.62-149.15)	<0.01
No. of lymph nodes analyzed	13 (0 - 46)	1.00 (0.99-1.01)	0.92
No. of postive lymph nodes	1 (0-43)	1.11 (1.09-1.13)	<0.01
Node category based on TNM7**			
N0	122 (37.3)	Reference	
N1	85 (26.0)	2.50 (1.71-3.65)	<0.01
N2	62 (19.0)	3.78 (2.54-5.61)	<0.01
N3	58 (17.7)	7.30 (4.89-10.90)	<0.01
Location of positive lymph nodes			
No positive lymph node	122 (37.3)	Reference	
Above diaphragm only	39 (11.9)	2.79 (1.78-4.39)	<0.01
Below diaphragm only	70 (21.4)	2.61 (1.75-3.88)	<0.01
Both above and below diaphragm	96 (29.4)	5.38 (3.76-7.70)	<0.01

Grade of differentiation			
Good	22 (6.7)	Reference	
Moderate	123 (37.6)	3.01 (1.39-6.52)	<0.01
Poor	162 (49.5)	4.77 (2.22-10.23)	<0.01
Unknown	20 (6.2)	1.21 (0.42-3.44)	0.72
Tumor location			
Middle 1/3	8 (2.4)	0.95 (0.41-2.16)	0.90
Lower 1/3	135 (41.3)	Reference	
Esophagogastric junction	184 (56.3)	0.93 (0.71-1.22)	0.58
Resection margin involvement***			
R0	255 (78.0)	Reference	
R1,R2 (any margin)	69 (21.1)	2.82 (2.09-3.80)	<0.01
Proximal margin only	3 (0.9)		
Distal margin only	8 (2.4)		
Circumferential margin only	57 (17.4)		
More than one margin	1 (0.3)		
Unknown	3 (0.9)	0.40 (0.06-2.84)	0.36
Neoadjuvant therapy			
No	220 (67.3)	Reference	
Chemotherapy only	62 (19.0)	0.56 (0.38-0.82)	<0.01
Radiotherapy only	2 (0.6)	1.79 (0.44-7.21)	0.42
Both	43 (13.1)	0.57 (0.37-0.88)	0.01
Surgical approach			
Transhiatal	313 (95.7)	Reference	
Transthoracic	14 (4.3)	1.89 (1.00-3.57)	0.05

* data shown are mean (SD)or median (range) or number (percentage); the sum of percentages may not equal 100 due to missing values or rounding.
** Node category according to 7th edition TNM-staging system: N0 (no positive nodes), N1 (1-2 positive nodes), N2 (3-6 positive nodes) and N3 (>6 positive nodes).
*** R0=resection margin microscopically tumor-free, >1mm; R1=resection margin macroscopically tumor-free, but microscopically <1mm; R2=macroscopically residual tumor.

Table 2
Hazard Ratios in a Cox regression model for patients staged according to both number (based on TNM7) and location of involved nodes relative to the diaphragm. Data are based on pathological findings as assessed in the resection specimens.

Pathological N stage	No nodes positive	1-2 nodes involved on one side of diaphragm	2 nodes involved on both sides of diaphragm	3-6 nodes involved on one side of diaphragm	3-6 nodes involved on both sides of diaphragm	>6 nodes involved on one side of diaphragm	>6 nodes involved on both sides of diaphragm
N/N*	50/122	55/77	6/8	17/24	35/38	8/8	50/50
Crude	Reference	2.46 (1.67-3.62)	2.96 (1.26-6.91)	2.79 (1.60-4.86)	4.58 (2.95-7.12)	7.42 (3.49-15.77)	7.32 (4.83-11.10)
Model**	reference	1.84 (1.22-2.77)	1.69 (0.70-4.10)	1.74 (0.94-3.21)	2.93 (1.79-4.79)	3.70 (1.67-8.22)	4.27 (2.64-6.92)

*no. of deaths/no. of cases
** Adjusted model : adjusted for age, T stage, differentiation, resection margin involvement, neoadjuvant therapy, surgical approach.

Table 3
Hazard Ratios in a Cox regression model for patients staged according location of involved nodes relative to the diaphragm as assessed by pretreatment EUS

EUS	Crude	Multivariate adjusted*	Crude	Multivariate adjusted*
No positive LN	Reference	Reference	Reference	Reference
Positive LNs on one side	1.25 (0.63-2.50)	1.40 (0.69-2.86)		
Positive LNs on both sides	2.44 (1.08-5.51)	2.95 (1.24-7.02)	2.13 (1.07-4.23)	2.38 (1.15-4.90)

* adjusting for age, gender, neoadjuvant chemoradiotherapy and study center

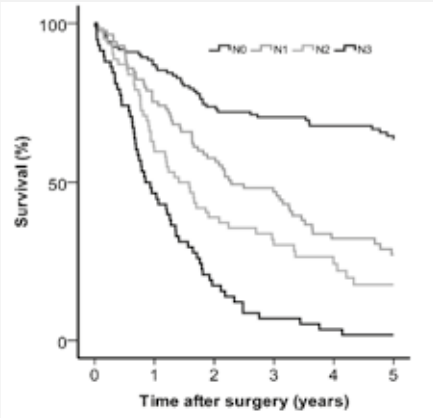
Supplementary table 1
Subset analysis describing the prognostic effect of nodal involvement on both sides of the diaphragm considering tumour location, transhiatal resection only, patients who did not receive neoadjuvant chemotherapy and surgical samples with 7 or more lymph nodes sampled.

	Event/n	Univariate analysis				Adjusted model*			
Tumour location		No Pos LN	Above	Below	Both	No Pos LN	Above	Below	Both
Total	221/327	Ref	2.79 (1.78-4.39)	2.61 (1.75-3.88)	5.38 (3.76-7.70)	Ref	1.72 (1.06-2.79)	1.66 (1.08-2.57)	2.22 (1.39-3.55)
Middle 1/3	6/8	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Lower 1/3	92/135	Ref	00	3.15 (1.67-5.94)	6.2 (3.46-11.27)	Ref	1.56 (0.71-3.45)	2.10 (1.01-4.36)	2.54 (1.06-6.07)
GOJ	123/184	Ref	2.90 (1.49-5.66)	2.63 (1.54-4.48)	5.38 (3.34-8.67)	Ref	2.11 (1.04-4.26)	1.67 (0.91-3.05)	2.24 (1.20-4.18)
Transhiatal resection only	211/313	Ref	2.79 (1.75-4.44)	2.75 (1.83-4.12)	5.43 (3.77-7.83)	Ref	1.73 (1.05-2.86)	1.85 (1.18-2.89)	2.25 (1.38-3.64)
More than 7 lymph nodes sampled in surgical specimen	181/273	Ref	3.22 (1.87-5.55)	3.07 (1.91-4.92)	6.93 (4.52-10.61)	Ref	2.05 (1.14-3.69)	1.87 (1.12-3.12)	2.88 (1.68-4.94)
No neoadjuvant therapy	144/195	Ref	3.12 (1.78-5.44)	3.34 (2.04-5.66)	6.26 (3.92-9.98)	Ref	2.00 (1.10-3.62)	1.72 (0.97-3.06)	2.57 (1.42-4.67)

* adjusted for age, number of positive LN, T stage, differentiation, resection margin involvement, neoadjuvant therapy, surgical approach, where appropriate.
The number of patients with tumours in the middle 1/3 of the oesophagus is too small to compute meaningful hazard ratio

Figure 1
Kaplan Meier overall survival curves of 327 patients stratified by (a) N-stage according to 7th edition TNM staging system, (b) by location of involved lymph nodes relative to the diaphragm and (c) by proposed combined lymph node staging system. Data are based on pathological findings as assessed in the resection specimens.

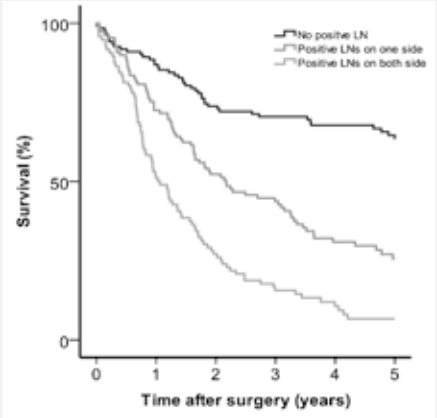
Figure 1 (a)



	No. of patient at risk		
years	0	2	4
N0	122	90	70
N1	85	49	22
N2	62	24	11
N3	58	10	2

Log Rank test: P<0.001

Figure 1 (b)

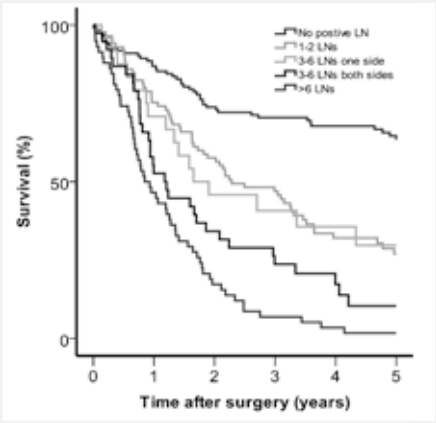


	No. of patient at risk		
years	0	2	4
No positive LN	122	90	70
Positive LN on one side	109	57	27
Positive LNs on both sides	96	26	8

Log Rank test: P<0.001

Figure 2
Kaplan Meier overall survival curves for 102 patients stratified by location of involved nodes relative to the diaphragm as assessed by preoperative EUS (Log Rank test: P=0.027)

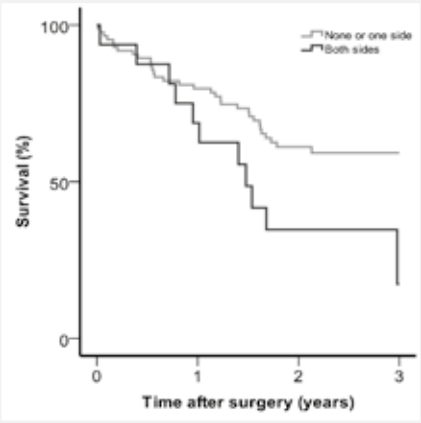
Figure 1 (c)



	No. of patient at risk		
years	0	2	4
No positive LN	122	90	70
1-2 LNs	85	49	22
3-6 LNs on one side	24	11	6
3-6 LNs on both sides	38	13	5
>6 LNs	58	10	2

Log Rank test: P<0.001

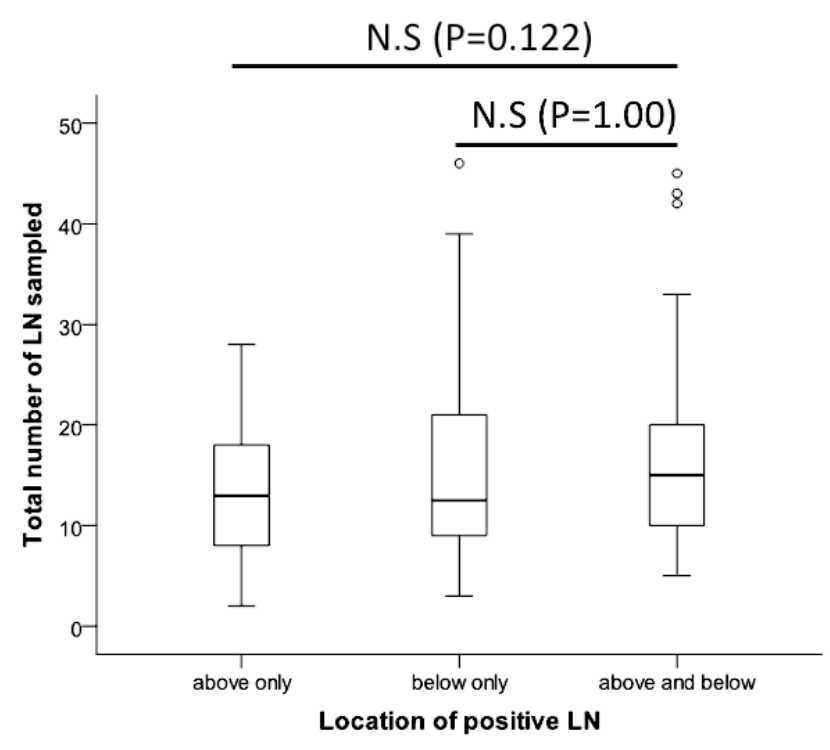
Figure 2



	No. of patient at risk			
years	0	1	2	3
No positive LNs or positive LNs on one side	86	65	37	11
Positive LNs on both sides	16	11	4	1

Log Rank test: P=0.027

Supplementary figure 1
Number of lymph nodes harvested in surgical samples of patients with lymph node involvement on one side of the diaphragm versus both sides of the diaphragm.



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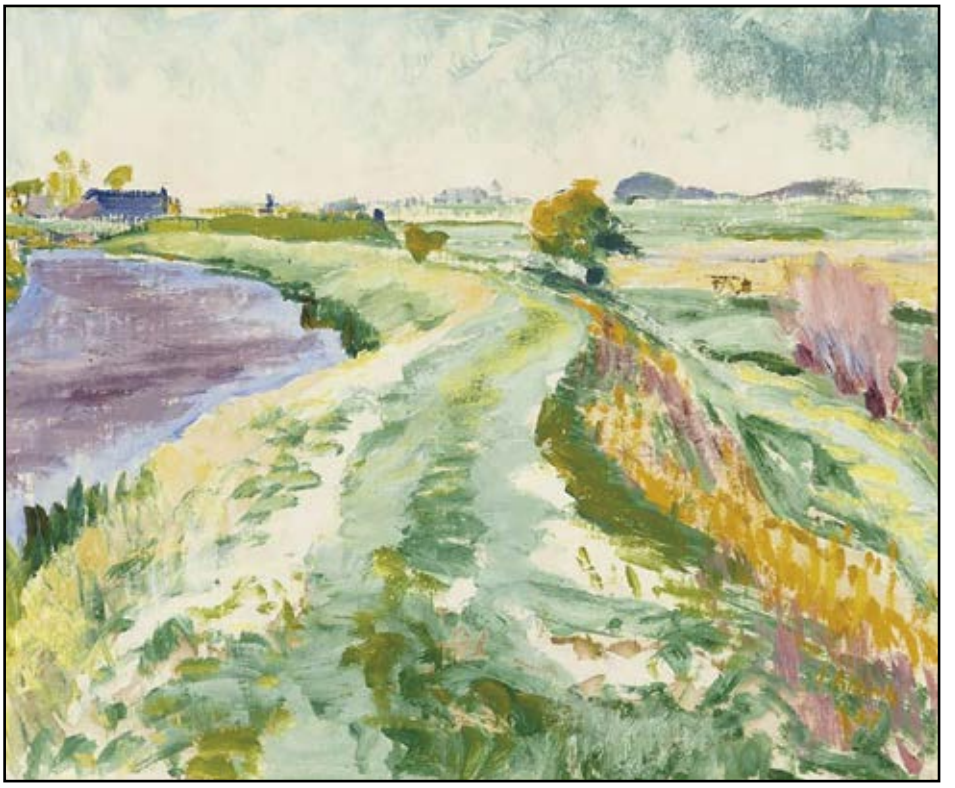

Chapter 4

Comparison of the 6th and 7th Editions of the UICC-AJCC TNM Classification for Esophageal Cancer

KOEN TALSMA, MD[1],
PIETER VAN HAGEN, MD[1],
BRECHTJE A. GROTENHUIS, MD, PHD[1],
EWOUT W. STEYERBERG, PHD[2],
HUGO W. TILANUS, MD, PHD[1], J
AN J. B. VAN LANSCHOT, MD, PHD[1],
BAS P. L. WIJNHOVEN, MD, PHD[1]

1 Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands;
2 Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Background

The new 7th edition of the Union for International Cancer Control–American Joint Committee on Cancer (UICC-AJCC) tumor, node, metastasis (TNM) staging system is the ratification of data-driven recommendations from the Worldwide Esophageal Cancer Collaboration database. Generalizability remains questionable for single institutions. The present study serves as a validation of the 7th edition of the TNM system in a prospective cohort of patients with pre-dominantly adenocarcinomas from a single institution.

Methods

Included were patients who underwent transhiatal esophagectomy with curative intent between 1991 and 2008 for invasive carcinoma of the esophagus or gastro-esophageal junction. Excluded were patients who had received neoadjuvant chemo(radio)therapy, patients after a noncurative resection and patients who died in the hospital. Tumors were staged according to both the 6th and the 7th editions of the UICC-AJCC staging systems. Survival was calculated by the Kaplan–Meier method, and multivariate analysis was performed with a Cox regression model. The likelihood ratio chi-square test related to the Cox regression model and the Akaike information criterion were used for measuring goodness of fit.

Results

A study population of 358 patients was identified. All patients underwent transhiatal esophagectomy for ade-nocarcinoma. Overall 5-year survival rate was 38%. Univariate analysis revealed that pT stage, pN stage, and pM stage significantly predicted overall survival. Prediction was best for the 7th edition, stratifying for all substages.

Conclusions

The application of the 7th UICC-AJCC staging system results in a better prognostic stratification of overall survival compared to the 6th edition. The fact that the 7th edition performs better predominantly in patients with adenocarcinomas who underwent a transhiatal surgical approach, in addition to findings from earlier research in other cohorts, supports its generalizability for different esophageal cancer practices.

INTRODUCTION

Accurate staging of cancer is important for stage-specific treatment, thus minimizing inappropriate treatment. Moreover, it allows for interinstitutional comparisons and disclosure of prognosis to patients.[1] The staging system for cancer in the esophagus and esophagogastric junction has been revised as outlined in the 7th edition of the Union for International Cancer Control/Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC), Cancer Staging Manual.[2]

Retrospective studies suggested that the number of involved lymph nodes is a better predictor of outcome than classifying lymph node involvement as either present or absent.[3,4] Peyre et al. showed that patients with 3 or more lymph nodes involved have a risk of systemic disease that exceeds 50%. When > 8 nodes are involved, the risk of dying is almost 100%.[5] Indeed, the latest 7th edition of the UICC-AJCC esophageal tumor, node, metastasis (TNM) staging system has acknowledged the importance of the number of involved nodes by revising the N category from site-dependent staging to a numerically based classification into N0 to N3. Another major change is the definition of regional lymph nodes.

The new UICC-AJCC staging system is the ratification of data-driven recommendations from a database of [7800 esophageal cancer patients created from a large multi-institutional collaboration involving 13 institutions.[6,7] This Worldwide Esophageal Cancer Collaboration (WECC) database overcomes problems of rarity of this cancer, but generalizability remains questionable for single institutions. WECC incorporates high-volume centers both from the West (where adenocarcinomas prevail) and from the East (where most tumors are squamous cell carcinomas). Moreover, the extent of intrathoracic lymph node dissection can vary greatly between different institutions, leading to potential bias.

The present study serves as a validation of the WECC-based 7th edition of the TNM system in a cohort of patients with both squamous cell carcinomas and adenocarcinomas from a single Western high-volume institution. Two studies already showed that the 7th edition criteria resulted in better prognostic stratification than the 6th edition.[8,9] However, both study cohorts consisted of squamous cell carcinomas or junctional tumors, respectively. Moreover, Gaur et al. included patients who received (neo)adjuvant therapy.[9]

The aim of this study was to assess the predictive ability of the 7th edition of the AJCC TNM staging system for overall survival and to compare this with the 6th edition in a cohort of patients who underwent transhiatal esophagectomy for adenocarcinomas without (neo) adjuvant therapy.

PATIENTS AND METHODS

Study Population

Included were all patients who underwent a transhiatal esophagectomy with curative intent between January 1991 and September 2008 at the Erasmus Medical Center (Rotterdam,

The Netherlands) for invasive squamous cell carcinoma and adenocarcinoma of the esophagus or gastroesophageal junction. Excluded were patients who had received neoadjuvant chemo(radio)therapy, patients after a noncurative (R1) resection (tumor-free margin\1 mm) and patients who died in the hospital. Clinicopathologic data of all patients had been routinely collected in an ongoing prospective registry.

Surgery

Transhiatal esophagectomy with cervical anastomosis was the chosen surgical approach in the present study. This encompasses the en-bloc dissection of the primary tumor and its adjacent lymph nodes under direct vision through the widened hiatus of the diaphragm up to the level of the inferior pulmonary vein. Subsequently, a 3–4-cm-wide gastric tube is created. The left gastric artery is transected at its origin with resection of celiac trunk lymph nodes. After mobilization and transection of the cervical esophagus, the intrathoracic middle and upper esophagus is bluntly dissected in an antegrade fashion with a vein stripper. Esophagogastrostomy is performed in the neck without a formal cervical lymphadenectomy.

Follow-up

Surviving patients were followed at regular intervals at the outpatient clinic until 5 years after surgery. Outpatient clinic visits encompassed history taking and physical examination. No routine imaging was performed. Recurrences were sought afterward, only when clinically indicated, by CT scan or ultrasound and proven by histology and cytology whenever possible. Overall survival was defined as the time between date of operation and date of death. Surviving patients were censored on the day of last follow-up. Patient survival status was calculated after contacting the general practitioners (performed by a trained data manager). The last follow-up checkpoint was July 2010. If follow-up was incomplete, survival was verified in the municipal mortality registers.

Statistical Analysis

Tumors were staged according to both the 6th and 7th editions of the UICC-AJCC staging systems. Survival was calculated by the Kaplan–Meier method, and differences between curves were assessed by the log rank test. Two multivariable models were built, one with the 6th edition and one with the 7th edition of the TNM staging system as categorical variables. The performance was tested for the model in which the stages were combined into four categories (I–IV) as well as for the model with all substages included (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV). A multivariable model with both 6th and 7th edition criteria included was used to assess the remaining value of the 6th edition when the 7th edition information was known.

The likelihood ratio chi-square test related to the Cox regression model was used for measuring goodness of fit. The Akaike information criterion (AIC) was applied to correct for the potential bias in comparing prognostic systems with different number of stages.[10,11] The -2 log likelihood (which is the parameter in the Cox regression) of the 6th edition was compared to that of the 7th edition; the smaller the value of this statistic, the better the model.

AIC was defined as: AIC = -2 log maximum likelihood + 2 x (the number of parameters in the model). A smaller AIC value indicates a more desirable model for predicting outcome. A value of $P<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 10 for Windows (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

A consecutive series of 766 patients underwent esophagectomy with curative intent. In total, 221 patients were excluded because they had received neoadjuvant chemo(radio)therapy in the context of a randomized, controlled trial.[12] Another 165 patients were excluded because of a noncurative (R1) resection, and 20 patients were excluded because of in-hospital mortality. Two patients had an in situ carcinoma and were also excluded from the current analysis. This resulted in a final study population of 358 patients. Mean follow-up was 51 months (median 37 months). Overall 5-year survival rate was 38%. Most recurrences of disease occurred within 2 years after surgery.

Patient characteristics and overall survival rates are summarized in Table 1. All patients underwent transhiatal esophagectomy for adenocarcinoma. Eight patients seemed to have distant metastasis during the operation; their disease was scored as M1.

Univariate analysis revealed that parameters pT stage, pN stage, and pM stage all significantly predicted overall survival. Except for histologic grade, no other significant predictors of survival were detected in this univariate analysis. The median number of dissected nodes per patient was 11. In patients with negative lymph nodes (pN0), the survival rates did not differ between patients with <=11 nodes and > 11 nodes dissected: 65% vs. 69%, respectively; $P = 0.65$; data not shown).

Stratification of Prognosis According to 6th and 7th Editions of TNM Staging Systems

The overall survival curves according to the N classifications of the 6th and 7th editions are shown in Fig. 1a and b, respectively.

Patient stage migration for reclassifying patients from the 6th to the 7th staging system and their survival rates are listed in Table 2. In 58% of the 358 esophageal cancer patients, stage did not differ in these two classification systems. Reassignment of disease stage occurred in all other patients, either to a higher or to a lower tier. According to the 6th edition staging system, 56 (87%) of 64 stage IV patients were staged as such because of a celiac lymph node metastasis. These patients were reclassified to a lower tier in the 7th edition: 6 of 64 were staged as stage IIB, 15 as stage IIIA, 19 as IIIB, and 16 as IIIC (Table 2).

The Kaplan–Meier curves of esophageal cancer patients based on the 6th and 7th editions of the TNM staging systems are depicted in Fig. 2. Both systems show a relatively ordered monotone distribution of survival. However, according to the 6th edition staging

system, the Kaplan– Meier plot shows overlapping curves for stage III and IV. In the 7th edition, no important overlapping occurs among stages I through IV.

Subgroup analysis among selected patients who had been considered to have stage IV disease according to the UICC-AJCC 6th edition scoring system showed that patients reclassified from stage IV disease to a lower tier in the UICC-AJCC 7th edition had a significantly better survival compared to patients still classified as stage IV according to the UICC-AJCC 7th edition. Moreover, the UICC-AJCC 7th edition was able to make further significant stratification of survival rates of these reclassified patients (Fig. 3; log rank P = 0.43).

The UICC-AJCC 7th edition staging system defines patients with positive paraesophageal cervical lymph nodes (n = 10) as having stage IIIA or IIIB disease. These patients, however, had a prognosis as bad as that of patients with distant metastasis (1-year overall survival rate 30% vs. 33%).

The performance of the 7th edition staging systems won quantified by the likelihood ratio chi-square and AIC (Table 3). Predictive ability was best for the full 7th edition criteria stratifying for all substages (highest likelihood ratio X2). AIC value was smaller for the 7th edition compared to the 6th edition staging system, indicating that it has a better prognostic stratification. The AIC value was lowest when patients with cervical lymph node metastasis at a large distance from the primary tumor (i.e., the lower third of the esophagus) were also classified as having stage IV disease. When the 6th and 7th edition staging systems are both included in one Cox regression model, the 6th edition no longer significantly predicted survival, whereas the 7th edition remained a significant stratifier of prognosis (data not shown).

DISCUSSION

This study shows that both the 6th and 7th UICC-AJCC TNM staging systems have a distinctive and monotone (ordered) relationship of stage group to overall survival for esophageal cancer patients who have undergone potentially curative surgery without (neo)adjuvant therapy. Distribution of patients among different stages is in line with that described in the literature. All groups are large enough for proper statistical analysis, except for stage IIA in the 7th edition.

Further testing of both systems on the present data shows that the 7th edition has the best performance because of the lowest AIC (i.e., a better fit) when Cox regression models are used. Survival curves stratified according to the UICC-AJCC 7th edition TNM staging system did not overlap, which is in contrast to the curves of the 6th edition. Moreover, further stratification of N stage according to number of positive lymph nodes in the 7th edition is indeed valuable, as shown in Fig. 1.

A major change in the new TNM staging system is the definition of regional lymph nodes. There has always been debate regarding the prognostic importance of positive celiac nodes, which were considered distant metastases in earlier editions.[13] In the 6th

edition staging system, the Kaplan–Meier plot showed overlapping curves for stage III and IV. According to the UICC-AJCC 7th edition, only patients with distant metastasis can be categorized as having stage IV disease. In contrast, according to the 6th edition, most stage IV disease was due to nonregional celiac lymph node metastasis, whereas stage IIB and III consisted of regional lymph node metastasis. Hence, 87% (56 of 64) of the patients with stage IV disease who were assessed according to the 6th edition criteria were reclassified as having stage IIB, IIIA, IIIB, and IIIC disease according to 7th edition criteria. Because these stages all had different survivals (Fig. 3), the present results support the new concept that it is unnecessary to identify nonregional lymph node metastasis and to label these nodes as M1A or M1B.

Two previous studies have compared the performance of 6th with the 7th editions of the TNM staging system in predicting survival. Hsu et al. evaluated 392 patients who underwent primary surgical resection through a tri-incisional approach in Taiwan during 1995–2006 [8] In the other study, nearly two-thirds of the patients received neoadjuvant therapy.[9] Both Hsu et al. and Gaur et al. concluded that the 7th edition of the staging system was a better model for pre-dicting outcome.[8,9] The most important difference with the present study is tumor histology; the vast majority of our patients had an adenocarcinoma, and almost all patients underwent a transhiatal resection.

The WECC-based 7th edition of the TNM staging sys-tem was built on data from patients without neoadjuvant treatment in a squamous cell carcinoma predominant database. Our sample population from a single institution is of course small compared with the worldwide esophageal cancer collaboration database, but the surgical procedures were highly uniform throughout the entire study period. The previous studies of Hsu et al. and Gaur et al., as well as the present study, underline the generalizability of the 7th edition and make it broadly applicable for daily clinical practice of esophageal cancer surgery around the world. [8,9]

The 7th edition of the UICC-AJCC esophageal TNM staging system has acknowledged the importance of the number of involved nodes by subdividing the N classification into N0 to N3. The transhiatal approach may profoundly affect the completeness of lymph node dissection and, accordingly, proper nodal staging. On the basis of data from a Dutch trial, nowadays, tumors proximal of esophagogastric junction (Siewert type 1) are preferably offered a transthoracic approach in our institution.[14,15] The latter approach will result in the collection of more lymph nodes and might give a more valid node sampling for staging. To which extent lymph nodes should be sampled for proper staging remains an important issue.[16] In a study performed by Peyre et al., the number of lymph nodes removed was an independent predictor of survival and a minimum number of 23 regional lymph nodes was pro-posed.[17] In the present study, the median number of nodes removed in a transhiatal approach was 11. This relatively scarce lymph node collection result can be seen as a drawback of our study, but it also gives rise to a remarkable finding. Although all patients underwent a transhiatal esophagectomy, the survival curves of different N stages (N0–N3; Fig. 1) do not overlap in our data, which probably indicates that there has been a valid and

robust node sampling. On the other hand, there seems to be a relatively large difference in survival rate between N0 and N1. We know from previous studies that there is a dichotomy in survival rate between tumors that did and did not lymphatically disseminate.[18] Early tumors (pT1) with lymph node invasion have prognosis comparable to tumors with more advanced T stage. Lymphatic dissemination is an independent indication of the biological aggressiveness of the tumor.

However, the large step in survival rate between N0 and N1 might also be due to a stage migrational effect. This, the so-called Will Rogers effect, means that stage N1 disease might actually include N2 or even N3 disease as a result of invalid node sampling.[19] The WECC group has indicated a resection of a minimum of 10 nodes for T1, 20 for T2, and >=30 nodes for T3–4 to be resected to obtain optimal results.[20] In N0 patients, such an effect does not occur; we found no significant difference in survival rates according to the number of resected lymph nodes in lymph node–negative patients. However, a median of 11 nodes definitely entails the risk of a stage migration effect in the patient group with positive nodes.

Finally, an important question remains: does a better predictive staging system have consequences for preoperative decision making? Medical decision making in terms of administering neoadjuvant chemotherapy and choosing the optimal surgical approach for esophagectomy is often based on clinical N staging. Lack of accurate preoperative staging is a major problem in allocating treatment modalities in these patients. It has been recently shown that further stratification according to the position of the positive node relative to the diaphragm can effectively discriminate between node-positive patients.[21] The overall accuracy for endoscopic ultrasound and CT in predicting the N stage per station is moderate, however. When the therapeutic approach depends on the status of a specific lymph node station, a more objective and reliable assessment of lymph nodal involvement (e.g., endoscopic ultrasound–fine-needle aspiration) should be considered.[22]

This study indicates that the application of the 7th UICC-AJCC staging system results in a better prognostic stratification of overall survival compared to the 6th edition. The fact that the 7th edition also has a superior prognostic ability in this study population from a single high-volume institution with predominantly adenocarcinomas and a two-incisional surgical approach supports its generalizability for different esophageal cancer practices.

Table 1
Patient demographics and results of univariate analysis for overall survival (N = 358)

Characteristic	Value	5-y survival, %	P
No. of patients	358		
Age, year, mean (range)	62.6 (28–83)	38.8	
Gender			
Male	293 (82%)	37.2	0.664
Female	65 (18%)	45.9	
pT			
1	78 (22%)	68.7	<0.001
2	79 (22%)	51.1	<0.001
3	201 (56%)	22.7	
pN			
0	146 (41%)	65.9	<0.001
1	90 (25%)	28.4	<0.001
2	81 (23%)	17.5	<0.001
3	41 (11%)	3.0	
pM			
0	350	39.7	<0.001
1	8	0.0	
Grade			
Well differentiated (G1)	31 (9%)	75.3	<0.001
Moderately differentiated (G2)	177 (49%)	39.4	<0.053
Poorly differentiated (G3)	150 (42%)	30.9	
Histology			
Squamous cell carcinoma	47 (13%)	41.9	0.752
Adenocarcinoma	311 (87%)	38.3	
Location			
Upper third	6 (2%)	30.4	0.352
Middle third	14 (4%)	42.6	0.325
Lower third (distal ? EGJ)	338 (94%)	36.9	
Type of surgical approach			
Transhiatal esophagectomy	358 (100%)		
Transthoracic esophagectomy			

T tumor stage (depth of invasion), N lymphatic dissemination stage (according to 7th edition of UICC-AJCC TNM staging system: N0 no positive lymph nodes, N1 1–2 positive lymph nodes, N2 3–6 positive lymph nodes, N3 C6 positive lymph nodes), M distant metastasis stage (according to 7th edition of UICC-AJCC TNM staging system: M0 no metastasis, M1 distant metastasis present), EGJ esophagogastric junction

Table 2
Cross table of staging esophageal cancer patients according to the 6th and 7th editions of UICC-AJCC TNM staging

6th edition[a]						5 year-survival according to 7th edition (%)
	I	IIA	IIB	III	IV	
7th edition[b]						
IA	43	0	0	0	0	87.7
IB	13	28	0	0	0	73.3
IIA	0	19	0	0	0	55.3
IIB	0	41	24	0	6	40.1
IIIA	0	0	21	50	15	24.3
IIIB	0	0	0	31	19	11.9
IIIC	0	0	4	20	16	3.1
IV	0	0	0	0	8	0.0
5 year-survival according to 6th edition (%)	81.9	56.8	38.3	14.1	12.4	

M1a celiac nodes involved in lower esophageal cancer or cervical nodes involved in upper esophageal cancer, M1b beyond locoregional node involvement (i.e., cervical nodes in lower esophageal cancer and celiac nodes in upper esophageal cancer; metastatic involvement of visceral organs, pleura, peritoneum)

[a] The 6th edition AJCC-UICC TNM staging system: stage I T_1N_0, stage IIA $T_{2,3}N_0$, stage IIB $T_{1,2}N_1$, stage III T_3N_1 or T_4N_0, stage IVA $T_{any}N_{any}$M1a, stage IVB $T_{any}N_{any}$M1b. The 7th edition AJCC-UICC TNM staging system (for adenocarcinoma): stage IA $T_1N_0G_{1,2}$, stage IB $T_1N_0G_3$ or $T_2N_0G_{1,2}$, stage IIA T_2N_0, stage IIB T_3N_0 or $T_{1,2}N_1$, stage IIIA T_4N_0 or T_3N_1 or $T_{1,2}N_2$, stage IIIB T_3N_2, stage IIIC $T_{any}N_3$ or $T_{4a}N_{1-3}$ or $T_{4b}N_{any}$, stage IV T_{any},N_{any},M_1

Table 3
Prognostic stratification of the 6th and 7th editions of the UICC-AJCC TNM staging systems

Model	Figure	Subgroups	LR v^2	AIC value[a]
6th edition	2a	I, II, III, IV	96.9	2607.1
7th edition, full	2b	IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV	128.6	2592.9
7th edition, collapsed		I, II, III, IV	99.0	2605.4

AIC Akaike information criteria, LR likelihood ratio

[a] A lower AIC value represents a better discriminatory model

Figure 1
Kaplan–Meier overall survival curves for 358 patients stratified by N stage according to a: 7th edition and b: 6th edition UICC-AJCC TNM staging systems (overall log rank P\0.01)

Figure 1 (a)

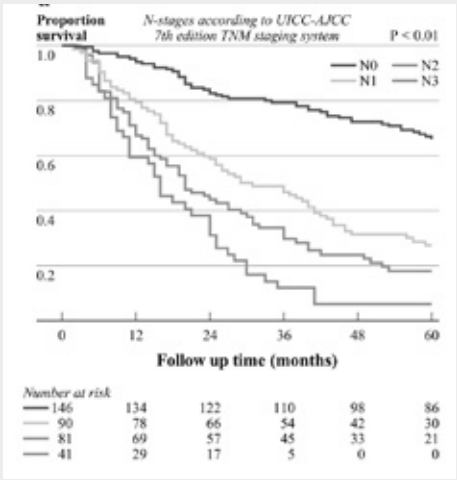


Figure 1 (b)

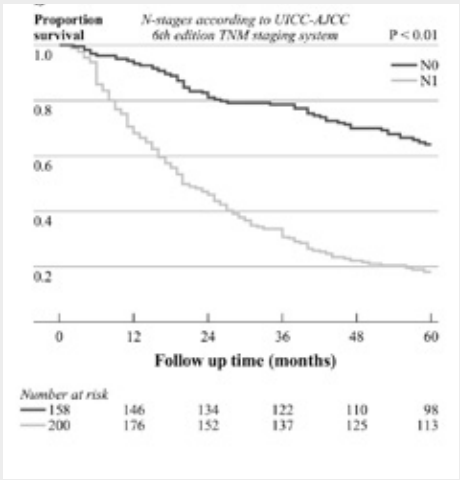


Figure 2
Kaplan–Meier curves of overall survival for 358patients stratified according to a: 6th edition and b: 7th edition UICC-AJCC TNM staging systems

Figure 2 (a)

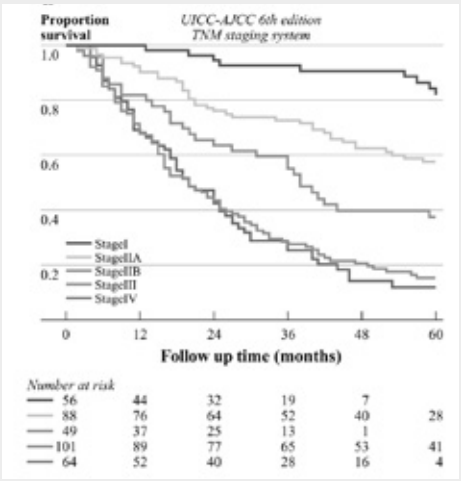


Figure 2 (b)

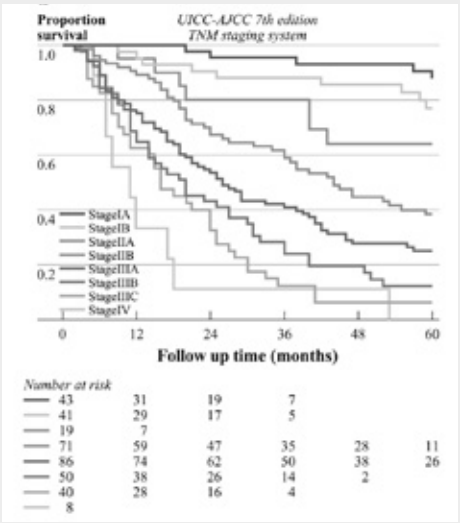
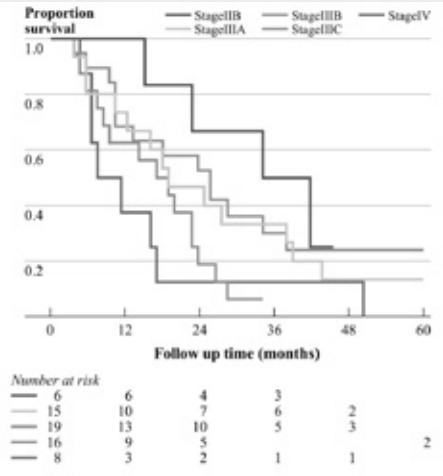


Figure 3
Kaplan–Meier overall survival curves for 64 UICC-AJCC 6th stage IV patients who were reclassified according to UICC-AJCC 7th edition TNM staging (log rank P = 0.43)



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Chapter 5

Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy; prognostic and therapeutic impact on survival

A. KOEN TALSMA MD[1]
JOEL SHAPIRO MD[1]
CASPAR W.N. LOOMAN PHD[2]
PIETER VAN HAGEN MD[1]
EWOUT W. STEYERBERG PHD[2]
ATE VAN DER GAAST MD, PHD[3]
MARK I. VAN BERGE HENEGOUWEN MD, PHD[4]
BAS P.L. WIJNHOVEN MD, PHD[1],
J. JAN B. VAN LANSCHOT MD, PHD[1]
- on behalf of the CROSS study group *

1 Departments of Surgery,
2 Public Health and
3 Medical Oncology, Erasmus MC -
University Medical Center, Rotterdam, The Netherlands.
4 Department of Surgery,
Academic Medical Center, Amsterdam, The Netherlands

*The members of the CROSS study group are listed at the end of the manuscript.

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ABSTRACT

Objectives

We aimed to examine the association between total number of resected nodes and survival in patients after esophagectomy with and without neoadjuvant chemoradiotherapy (nCRT).

Background data

Most studies concerning the potentially positive effect of extended lymphadenectomy on survival have been performed in patients who underwent surgery alone. As nCRT is known to frequently 'sterilize' regional nodes, it is unclear whether extended lymphadenectomy after nCRT is still useful.

Methods

Patients from the randomized CROSS-trial who completed the entire protocol (i.e. surgery alone or chemoradiotherapy plus surgery) were included. With Cox regression models we compared the impact of number of resected nodes as well as resected positive nodes on survival in both groups.

Results

161 patients underwent surgery alone and 159 patients received multimodality treatment. Median (interquartile range) number of resected nodes was 18(12-27) and 14(9-21), with 2(1-6) and 0(0-1) resected positive nodes respectively. Persistent lymph node positivity after nCRT had a greater negative prognostic impact on survival as compared to lymph node positivity after surgery alone. Total number of resected nodes was significantly associated with survival for patients in the surgery alone arm (hazard ratio (HR) per 10 additionally resected nodes, 0.76; p=0.007), but not in the multimodality arm (HR 1.00; p=0.98).

Conclusions

The number of resected nodes had a prognostic impact on survival in patients after surgery alone, but its therapeutic value is still controversial. After nCRT, number of resected nodes was not associated with survival. These data question the indication for maximization of lymphadenectomy after nCRT.

INTRODUCTION

Esophageal cancer is associated with early and chaotic lymphatic dissemination to both the neck, chest and abdomen [1, 2]. The lymphadenectomy accompanying esophagectomy is the main oncological factor that can be influenced by the surgeon, besides a complete resection of the primary tumor. Many investigators have previously attempted to explore the potential benefits of extended lymphadenectomy which include more accurate disease staging, better locoregional disease control, and perhaps even improved long-term survival. For staging purposes a more extended lymphadenectomy is intuitively superior to a more limited nodal dissection [3, 4]. The therapeutic impact of extended lymphadenectomy in esophageal cancer surgery, however, has remained controversial. Some authors state that surgery has reached its maximum therapeutic impact with limited lymphadenectomy, while others believe that the course of the disease can be influenced favorably by aggressive surgery with a more extended lymphadenectomy [5, 6]. Although most studies have concluded that lymph node retrieval is associated with improved survival, the majority of these studies have been performed in patients undergoing surgery alone, which has led to recommendations regarding the optimal extent of lymphadenectomy ranging from 6-30 nodes [7, 8]. Other studies investigated designated fields of dissection [3, 4]. Prospective trials have been performed comparing survival after transhiatal and transthoracic esophagectomy [9], but a recent meta-analysis did not show any difference in survival between limited transhiatal and extended transthoracic operations [10].

Especially after publication of the randomized controlled CROSS trial [11], neoadjuvant chemoradiotherapy (nCRT) has become standard of care for esophageal cancer patients in many countries. As nCRT is known to frequently 'sterilize' regional nodes, it is unclear whether extended lymphadenectomy after nCRT is still indicated for prognostic and therapeutic reasons. The aim of the present study was, therefore, to examine the association between the total number of resected nodes and survival in patients with esophageal cancer undergoing surgical resection with and without nCRT.

METHODS

Study population and follow-up

The study population consisted of patients who participated in the randomized CROSS-trial from March 2004 through December 2008 [11]. Patients with histologically confirmed, potentially curable carcinoma of the esophagus or esophagogastric junction were randomly assigned to receive surgery alone or neoadjuvant chemoradiotherapy followed by surgery. The randomization process was stratified for histological tumor type, center and clinical N-stage. Patients were excluded who underwent exploratory thoracotomy or laparotomy only. Follow-up took place at regular intervals with a minimal follow-up of 24 months.

Clinical and pathological staging

Pretreatment clinical staging included endoscopy (and ultrasonography) with biopsy and CT of the neck, chest, and upper abdomen; and external ultrasonography of the neck, with fine-needle aspiration of suspected cervical lymph nodes. The surgical resection specimen was processed according to a standardized protocol. The clinical and pathological staging were based on the 6th and 7th edition of the TNM staging system respectively [12]. Tumor regression after nCRT was classified in the resection specimen as major response: ≤10% viable tumor cells and minor response: >10% viable tumor cells.

Neoadjuvant treatment and surgical approach

Patients randomized to neoadjuvant treatment underwent weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/ml/min) and paclitaxel (50 mg/m2) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days/week), followed by surgery.

For esophageal carcinomas at or above the level of the carina a transthoracic esophagectomy (TTE) with two-field lymph node dissection was performed. For carcinomas located well below the level of the carina, either a TTE with two-field lymph node dissection or a transhiatal esophagectomy(THE) was performed. THE encompassed en bloc dissection of the primary tumor and its adjacent lymph nodes under direct vision through the widened diaphragmatic hiatus up to the level of the inferior pulmonary vein. Dissected lymph nodes in the upper abdomen included the paracardial, lesser curvature, left gastric artery, celiac trunk, common hepatic artery, and splenic artery nodes. TTE included en bloc dissection of the azygos vein, thoracic duct, ipsilateral pleura, and all peri-esophageal tissue in the posterior mediastinum. Compared to THE, the resection specimen after TTE additionally included the middle mediastinal, subcarinal, paratracheal and aortopulmonary window lymph nodes. In the present study, 'extended' lymphadenectomy was defined in terms of numbers of lymph nodes retrieved.

Statistical analysis

Descriptive statistics included median and interquartile range for continuous variables and percentages for categorical variables. Mann-Whitney, Chi-square, and log-rank tests were used to assess statistical significance ($p<0.05$, two-sided). Overall survival was defined as the time interval between day of randomization and day of censoring or death and analysed with Kaplan-Meier and Cox regression analysis. Scatter plots of number of resected nodes versus number of resected positive nodes were constructed separately for both randomization arms. In these scatter plots, lines were fitted representing equal probabilities of death as calculated with Cox regression models. All analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL, USA) and R (version 2.14, R foundation for statistical computing, Vienna, Austria).

RESULTS

Patient and tumor characteristics

Of 368 patients enrolled in the original CROSS trial, 180 were randomly assigned to nCRT+surgery, and 188 to surgery alone. In the nCRT+surgery group 161 patients actually underwent resection, of whom two patients were excluded from the present analysis because of missing values on the exact number of resected nodes. In the surgery alone group 161 actually underwent resection. In both groups, two out of three patients had signs of lymph node involvement during pretreatment investigations (Table 1). Both groups were similar in the surgical approaches that were chosen. nCRT resulted in clear downstaging; in almost forty percent of patients no vital tumor cells were identified in the esophageal wall after nCRT (ypT0). R0 resection rate increased from 69% in the surgery alone group to 93% in the nCRT+surgery group ($p<0.01$).

Impact of nCRT on number of resected nodes and number of resected positive nodes

The distribution of the number of resected nodes for both randomization groups is presented in Figure 1, showing a leftward shift (i.e. fewer resected nodes) in the nCRT+surgery group. Median number (interquartile range) of resected nodes was 18(12-27) for the surgery alone group and 14(9-21) for the nCRT+surgery group (Table 1). Mean difference in number of resected nodes between the surgery alone and nCRT+surgery group was 4.3 ($p<0.001$). Number of resected nodes was not associated with radicality of resection in both groups (data not shown).

Median number (interquartile range) of resected positive nodes for the surgery alone and nCRT +surgery group was 2(1-6) and 0(0-1) respectively (Table 1), resulting in a leftward shift in the 7th TNM N-stage distribution of the nCRT+surgery group (Supplementary figure 1). Fewer positive nodes (mean difference, 3.4 nodes; $p<0.001$), but a comparable number of negative nodes (mean difference, 1.0 nodes; $p=0.37$) were resected in the nCRT+surgery group as compared to the surgery alone group (Supplementary figure 2).

Impact of number of resected nodes on number of resected positive nodes

In the surgery alone group a positive association was identified between number of resected nodes and number of resected positive nodes. This association was absent in the nCRT+surgery group (Figure 2). The mean number of resected positive nodes in patients who underwent surgery alone ranged from 2.4 in patients with 0-10 resected nodes to 5.9 in patients ≥25 resected nodes.

Impact of number of resected (positive) nodes on survival

For surviving patients, the median follow-up was 48.7 months (range 25.5-80.9). The overall survival rate at 5 year was 44%, with 37% in the surgery alone group as compared to 50% in the nCRT+surgery group ($p=0.004$).

At univariable analysis, age, ypT-stage, resection margin involvement and number of resected positive nodes tended to be associated with survival in both groups (Table 2). In multivariable Cox regression analysis, the number of resected nodes was significantly associated with survival (HR 0.76 per every 10 additionally resected nodes; $p<0.01$) in patients who underwent surgery alone. However, in the nCRT+surgery group, number of resected nodes was not associated with survival (HR 1.00, $p=0.87$), nor was it associated with survival within ypN0, ypN1 or ypN1-ypN3 patients (data not shown). The number of resected positive nodes was associated with survival in both groups, but lymph node positivity after nCRT was associated with a more negative impact on survival compared to lymph node positivity after surgery alone (HR 1.18 vs HR 1.12 per every additionally resected positive node, respectively), especially in combination with a minor pathological response to nCRT (HR 1.38, $p<0.05$; data not shown). Additionally, a stratified analysis for histological tumor type showed that the significant impact of number of resected nodes observed in adenocarcinoma patients treated by surgery alone (every 10 additionally resected nodes HR=0.71; $p<0.05$) disappeared after nCRT (HR=1.06; n.s.). In the group of squamous cell carcinoma patients there was a similar (smaller) effect after nCRT, but sample sizes were probably too small to reach significance (surgery alone: HR=0.73; n.s. vs. nCRT+surgery: HR=0.84; n.s.).

In Figure 3 scatter plots are shown that depict the same correlation between number of resected nodes and number of resected positive nodes as is visualized in Figure 2, but now for all individual patients. At a given number of resected positive nodes, the probability of death in the surgery alone group will become lower when the number of resected nodes increases (Figure 3A), but will remain unchanged and will even tend to become higher in the nCRT+surgery group (Figure 3B).

DISCUSSION

After nCRT, the number of resected nodes and number of resected positive nodes were significantly decreased, as compared to the surgery alone group. Also, the positive correlation between number of resected nodes and number of resected positive nodes, which was significant in the surgery alone group, was not present in the nCRT+surgery group. The number of resected nodes was an independent prognostic factor for survival in patients who underwent surgery alone, but not in patients treated with nCRT followed by surgery. The addition of nCRT to surgery resulted in a significantly reduced number of resected positive nodes, but after this multimodality treatment node positivity was more strongly inversely associated with survival than after surgery alone.

Prognostic implications of number of resected nodes

Identifying positive nodes is informative for a patient's prognosis. In the present study, the decreased number of nodes retrieved in the nCRT+surgery group resulted exclusively from a reduction in number of resected positive nodes, while the number of resected negative

nodes was similar in both groups (Supplementary figure 2). This might be because many positive nodes are sterilized by nCRT [13]. Therefore, many initially positive nodes will contribute to the node negative category in the resection specimen after nCRT. The overall decrease in nodes resected after nCRT might therefore be compensated in the node negative category by the addition of formerly positive (i.e. sterilized) nodes. Interestingly, not only did the number of resected nodes and number of resected positive nodes decrease upon addition of nCRT to surgery, also the "upstaging" effect of number of resected nodes on number of resected positive nodes disappeared (Figure 2). This (absent) correlation suggests that the number of resected positive nodes found after nCRT is less dependent on sampling compared to resected positive nodes found after surgery alone.

In patients treated with surgery alone, the number of resected nodes was not correlated with overall survival in univariable analysis. However, in multivariable analysis, after correction for the number of resected positive nodes, the number of resected nodes did show an independent association with overall survival (Table 2). The difference in association from univariable to multivariable analysis is most likely caused by the dominant and confounding effect of resected positive nodes. Thus, after correction for the number of resected positive nodes, the smaller but significant prognostic effect of number of resected nodes is revealed.

For patients undergoing nCRT plus surgery, however, neither in univariable analysis, nor in multivariable analysis an association was found between the number of resected nodes and overall survival. Apparently, the prognostic value of the total number of resected nodes for survival is lost in patients treated with nCRT +surgery, even after correction for the number of resected positive nodes.

In the CROSS trial, the favorable effect of nCRT on lymph node positivity has been clearly shown: in the surgery alone group 76% of patients were pathologically node positive, versus 32% in the nCRT+surgery group. However, lymph node positivity in the nCRT+surgery group in itself tended to have a stronger negative prognostic impact on survival as compared to that in the surgery alone group. Apparently, persistent lymph node positivity after nCRT reflects a biologically unfavorable tumor biology, which is in line with previous publications [14-17].

Therapeutic considerations

After correction for the number of resected positive nodes, the number of resected nodes was significantly associated with survival in the surgery alone group (Table 2). Removal of negative nodes might hence have not only a prognostic impact, but also a therapeutic impact in this group. The most important hypothesis supporting such genuine survival benefit of an extended lymphadenectomy is the clearance of micrometastases that can be present in up to 50% of histology-negative nodes and are associated with a poor outcome [18-20].

Some previous studies have shown that increasing the number of resected nodes is still relevant after nCRT [21-23], while other studies have concluded that it is not. [16, 24-26] In the present data, within the nCRT+surgery group, no such prognostic impact of the number of resected nodes could be identified, let alone any therapeutic impact on survival.

This could possibly be explained by the sterilization of micrometastases after chemoradiotherapy.[27]

Some authors question any therapeutic impact of extended lymphadenectomy. In their view, lymph node metastases are simply markers of systemic disease and removal of the primary lesion plus the easily accessible peritumoral nodes alone will yield a similar survival [28]. Their alternative explanation is that the suggested therapeutic effect is based on stage migration. Stage migration occurs when positive nodes in the extended part of the dissection change N-stage to a higher category (surgery alone group in Figure 2), but at the same time have a more favorable prognosis than patients with a similar number of positive nodes from a more limited dissection (the so-called 'Will Rogers phenomenon' [29]). This 'stage purification' leads to unreliable stage-by-stage comparisons of survival.

In the present study, 'extended lymphadenectomy' was defined in terms of numbers of lymph nodes retrieved, which is a more reliable variable to study compared to surgical approach, which is not always synonymous with extent of lymph node stations sampling. Unfortunately, data on the exact location of lymph node stations from which individual lymph nodes were retrieved were not available. The strength of the present study is that patients were randomized. Therefore, the described difference in impact of the number of resected nodes on survival between both arms can be attributed to neoadjuvant chemoradiotherapy specifically. The multicenter design is both a strength (because of great variability and therefore generalizability) and a limitation (since there was no strict protocol for surgical approach nor for extent of lymph node stations sampling). To properly address the impact of surgical approach on lymph node retrieval and survival, a new randomized trial should be performed comparing a transhiatal and transthoracic approach after nCRT. Finally, the relatively small number of patients per randomization arm limited the statistical power.

In conclusion, lymph node positivity, especially if persistent after nCRT, is a strong negative prognostic factor for overall survival. The number of resected lymph nodes has an independent prognostic impact on survival in patients who undergo surgery alone. The therapeutic value of extended lymphadenectomy, however, remains questionable in this group. After nCRT, the number of resected nodes is not associated with survival. These data question the indication for maximization of lymph node dissection after nCRT for staging purposes as well as for therapeutic reasons.

CROSS Study Group

In addition to the authors, the following persons participated in the CROSS-trial:
The authors' full names, degrees and affiliations are as follows:

- Maarten C.C.M. Hulshof, M.D., Ph.D., Dept. of Radiation Oncology, Academic Medical Center, Amsterdam
- Hanneke W. M. van Laarhoven, M.D., Ph.D., Dept. of Medical Oncology, Academic Medical Center, Amsterdam
- Grard A.P. Nieuwenhuijzen, M.D., Ph.D., Dept. of Surgery, Catharina Hospital, Eindhoven
- Geke A.P. Hospers, M.D., Ph.D., Dept. of Medical Oncology, University Medical Center Groningen, Groningen
- Johannes J. Bonenkamp, M.D., Ph.D., Dept. of Surgery, Radboud University Medical Center, Nijmegen
- Miguel A. Cuesta, M.D., Ph.D., Dept. of Surgery, VU Medical Center, Amsterdam
- Reinoud J.B. Blaisse, M.D., Dept. of Medical Oncology, Rijnstate Hospital, Arnhem
- Olivier R.C. Busch, M.D., Ph.D., Dept. of Surgery, Academic Medical Center, Amsterdam
- Fiebo J.W. ten Kate, M.D., Ph.D. Dept. of Pathology, Academic Medical Center, Amsterdam
- Geert-Jan Creemers, M.D., Ph.D., Dept. of Medical Oncology, Catharina Hospital, Eindhoven
- Cornelis J.A. Punt, M.D., Ph.D., Dept. of Medical Oncology, Radboud University Medical Center, Nijmegen
- John T.M. Plukker, M.D., Ph.D., Dept. of Surgery, University Medical Center Groningen,Groningen
- Henk M.W. Verheul, M.D., Ph.D., Dept. of Medical Oncology, VU Medical Center, Amsterdam
- Herman van Dekken, M.D., Ph.D., Dept. of Pathology, St. Lucas Andreas Hospital, Amsterdam
- Maurice J.C. van der Sangen, M.D., Ph.D., Dept. of Radiation Oncology, Catharina Hospital, Eindhoven
- Tom Rozema, M.D., Dept. of Radiation Oncology, Radboud University Medical Center, Nijmegen and Verbeeten Institute Tilburg, Tilburg
- Katharina Biermann, M.D., Ph.D. Dept. of Pathology, Erasmus MC - University Medical Center, Rotterdam
- Jannet C. Beukema, M.D., Dept. of Radiation Oncology, University Medical Center Groningen, Groningen
- Anna H.M. Piet, M.D., Dept. of Radiation Oncology, VU Medical Center, Amsterdam
- Caroline M. van Rij, M.D., Dept. of Radiation Oncology, Erasmus MC - University Medical Center, Rotterdam
- Janny G. Reinders, M.D., Dept. of Radiation Oncology, Radiotherapeutic Institute, Arnhem
- Hugo W. Tilanus, M.D., Ph.D. Dept. of Surgery, Erasmus MC - University Medical Center, Rotterdam

Table 1
Clinical and tumor characteristics of 320 patients with esophageal or junctional cancer who underwent surgical resection with or without neoadjuvant chemoradiotherapy (nCRT) in the CROSS trial[11]

	Surgery Alone (N=161)	nCRT + Surgery (N=159)
Age – median [years] (interq. range)	60 (54-66)	60 (55-67)
Male sex – no. (%)	129 (80.1)	121 (76.1)
Tumor type –no. (%)		
Squamous cell carcinoma	37 (23.0)	37 (23.3)
Adenocarcinoma	121 (75.2)	119 (74.8)
Other	3 (1.9)	3 (1.9)
Tumor location –no. (%)		
Proximal third esophagus	3 (1.9)	2 (1.3)
Middle third esophagus	16 (9.9)	24 (15.1)
Distal third esophagus	123 (76.4)	111 (69.8)
Esophago-gastric junction	18 (11.2)	22 (13.8)
Not specified	1 (0.6)	-
Differentiation grade in biopsy –no. (%)		
Well differentiated	11 (6.8)	5 (3.1)
Moderately differentiated	73 (45.3)	50 (31.4)
Poorly differentiated	69 (42.2)	68 (42.8)
Not specified	8 (5.0)	36 (22.6)
Clinical N-stage (TNM6)* –no. (%)		
cN0	53 (32.9)	56 (35.2)
cN1	100 (62.1)	101 (63.5)
Not specified	8 (5.0)	2 (1.3)
Operative approach‡ –no. (%)		
TTE	87 (54.0)	88 (55.3)
THE	72 (44.7)	71 (44.7)

Other	2 (1.2)	
Complete pathological response –no. (%)	n/a	47 (29.6)
(y)pT stage (TNM7†)		
0/is	-	62 (39.0)
1	13 (8.1)	15 (9.4)
2	19 (11.8)	32 (20.1)
3	126 (78.3)	48 (30.2)
4	3 (1.9)	1 (0.6)
Not specified		1 (0.6)
Resection margin involvement∞ –no. (%)		
R0	111 (68.9)	147 (92.5)
R1	49 (30.4)	12 (7.5)
Not specified	1 (0.6)	
(y)pN stage (TNM7ϕ) –no. (%)		
0	39 (24.2)	108 (67.9)
1	43 (26.7)	35 (22.0)
2	41 (25.5)	11 (6.9)
3	38 (23.6)	5 (3.1)
Number of resected nodes – median no. (interq. range)	18 (12-27)	14 (9-21)
Number of resected positive nodes – median no. (interq. range)	2 (1-6)	0 (0-1)

* Clinical lymph-node (N) stage was assessed by means of endoscopic ultrasonography, CT, or 18F-fluorodeoxyglucose positron-emission tomography and was classified according to 6th edition of the UICC TNM classification; ‡TTE=transthoracic esophagectomy; THE=transhiatal esophagectomy; † Pathologic TNM stage was classified according to the 7th edition of the UICC TNM staging system; ∞R0=resection margin microscopically tumor-free, ≥ 1mm; R1=resection margin macroscopically tumor-free, but microscopically <1mm;ϕ Pathologic node category according to 7th TNM-staging system: N0 (no positive nodes), N1 (1-2 positive nodes), N2 (3-6 positive nodes) and N3 (>6 positive nodes).

Table 2
Hazard ratios (HR) for overall survival from univariable and multivariable Cox-regression analysis in 320 esophageal or junctional cancer patients who underwent surgical resection with or without neoadjuvant chemoradiotherapy (nCRT) in the CROSS trial[11]

		Univariable analysis (HR (95% CI))		Multivariable analysis (HR (95% CI))	
	Category	**Surgery-alone**	**nCRT+surgery**	**Surgery-alone**	**nCRT+surgery**
Age	Every 10 additional years	1.28 (1.03-1.60)	1.16 (0.90-1.51)	1.20 (0.94-1.52)	1.26 (0.93-1.70)
(y)pT stage	0 / *in situ*	n/a	0.48 (0.29-0.81)	n/a	0.55 (0.32-0.95)
	ypT1	0.12 (0.03-0.50)	0.64 (0.28-1.44)	0.14 (0.03-0.59)	0.64 (0.28-1.51)
	ypT2	0.56 (0.30-1.06)	0.55 (0.31-1.01)	0.80 (0.42-1.54)	0.44 (0.23-0.85)
	ypT3	1 (ref)	-	-	-
	ypT4	0.28 (0.04-2.04)	7.11 (0.92-54.84)	0.25 (0.03-1.69)	5.44 (0.62-47.74)
Resection margin involvement	R0	1 (ref)	-	-	-
	R1	1.34 (0.90-2.00)	1.62 (0.78-3.38)	1.42 (0.93-2.10)	1.20 (0.53-2.73)
Number of resected nodes	Every 10 additionally resected nodes	0.95 (0.79-1.14)	1.02 (0.84-1.25)	0.76 (0.61-0.95)	1.00 (0.84-1.25)
Number of resected positive nodes	Every additionally resected positive node	1.11 (1.08-1.15)	1.15 (1.06-1.25)	1.12 (1.08-1.16)	1.18 (1.07-1.29)

Figure 1
Distribution of number of resected lymph nodes as assessed in the resection specimen of patients who underwent surgery alone (n=161) or neoadjuvant chemoradiotherapy (nCRT) followed by surgery (n=159). Compared to the surgery alone group, a leftward shift (*i.e.* fewer resected nodes) was observed in the nCRT+surgery group.

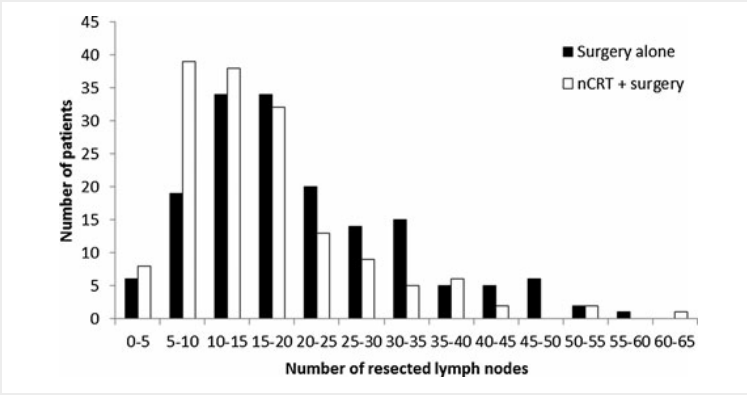


Figure 2
Correlation between number of resected nodes (quartiles) and mean number (95% confidence interval) of resected positive nodes in patients who underwent surgery alone (n=161) or chemoradiotherapy (nCRT) followed by surgery (n=159).

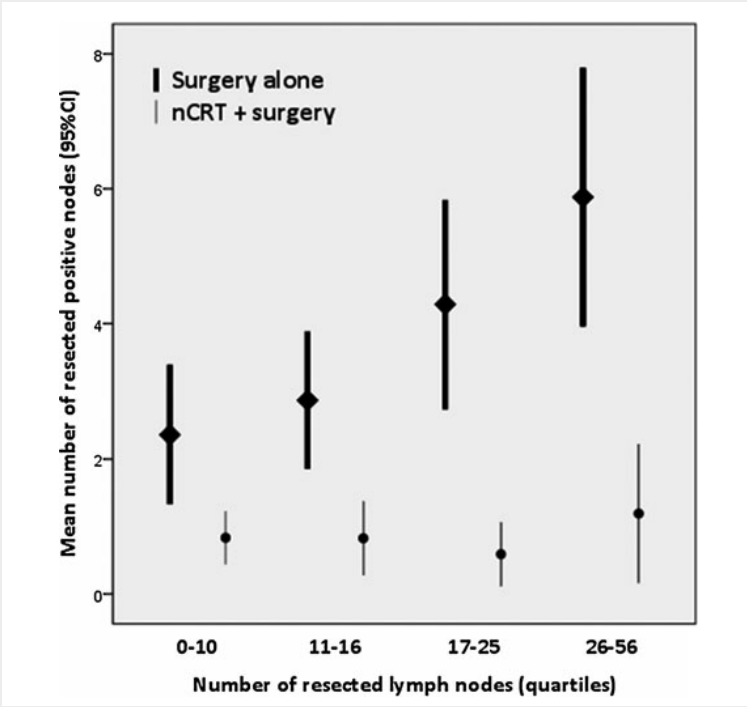
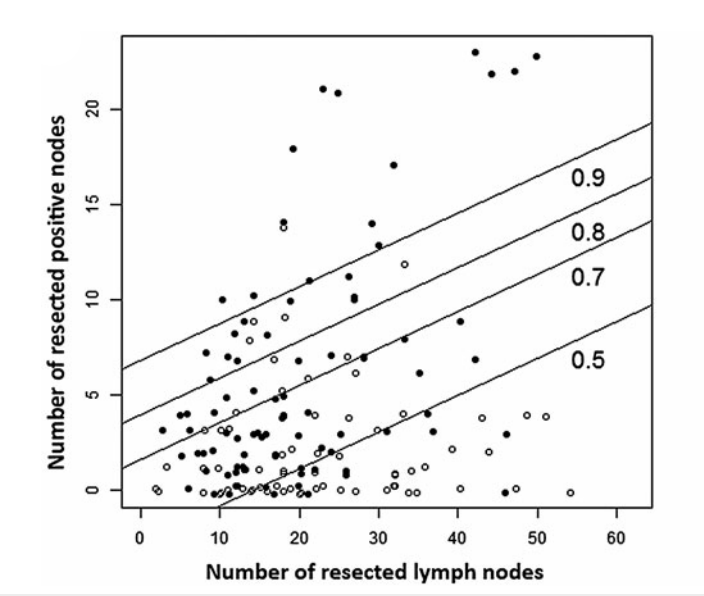


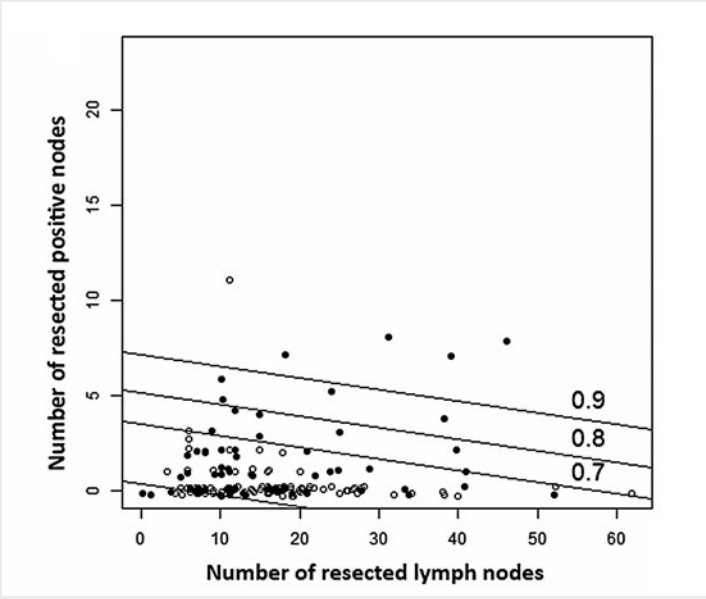
Figure 3
Correlation between number of resected nodes and number of resected positive nodes in individual patients who underwent surgery alone (A: n=161) or neoadjuvant chemoradiotherapy (nCRT) followed by surgery (B: n=159). Open circles indicate patients who were alive at end of follow-up; closed circles indicate patients who had died at end of follow-up.

Figure 3 (a)

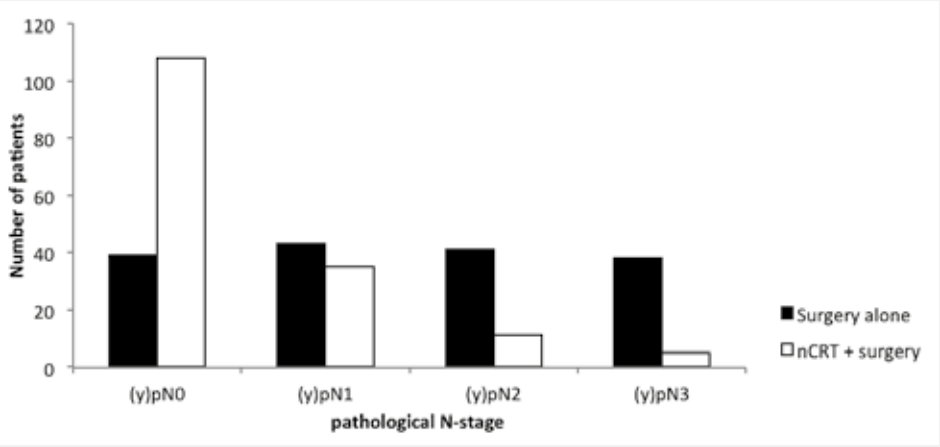


Legend figure 3
Lines represent equal probabilities of death as can be calculated by the proportion of closed (dead) and open (alive) circles. In both groups (A and B), an increase in the number of resected positive nodes results in a higher probability of death. In the patients who underwent surgery alone, lines are sloped *i.e.* at a given number of resected positive nodes more resected nodes in the specimen are associated with a decreased probability of death (A). In patients in the nCRT+surgery group, the probability lines have a more horizontal course, *i.e.* at a given number of resected positive nodes more resected nodes are not associated (and even tend to be positively associated) with probability of death (B).

Figure 3 (b)

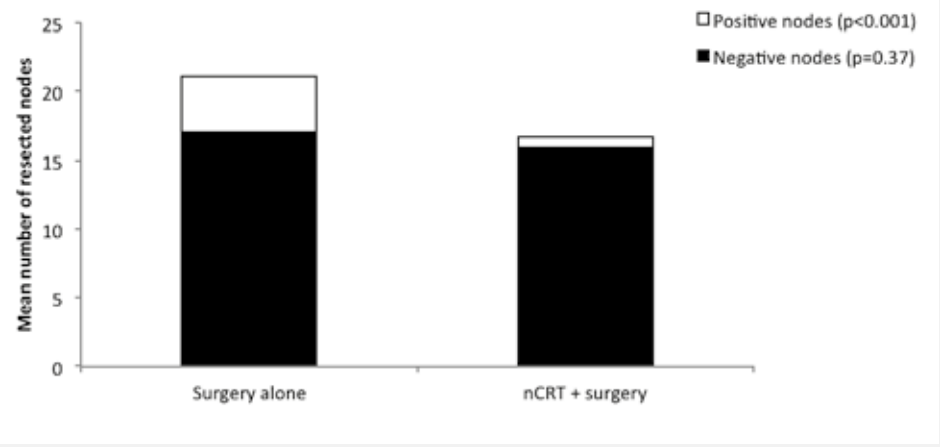


Supplementary figure 1
Pathological N-stage according to 7th edition of TNM staging system as assessed in patients who underwent surgery alone (n=161) or neoadjuvant chemoradiotherapy (nCRT) followed by surgery (n=159). Data indicate a leftward shift (i.e. fewer resected positive nodes) in the nCRT+surgery group.



N0 = no positive lymph nodes; N1 = 1-2 positive lymph nodes; N2 =3-6 positive lymph nodes; N3 = more than 6 positive lymph nodes.

Supplementary figure 2
Comparison of mean number of positive and negative lymph nodes as assessed in the resection specimen of patients who underwent surgery alone (n=161)or neoadjuvant chemoradiotherapy (nCRT) followed by surgery(n=159).



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5

LETTER TO THE EDITOR

Neoadjuvant Therapy and Lymphadenectomy in Esophageal Cancer: Both Are Essential to Maximize Survival Benefit

To the Editor:

We read with great interest the article by Talsma et al.[1] The authors addressed the role of extended lymphadenectomy after neoadjuvant chemoradiotherapy (CRT) for esophageal cancer. The study population in this article consisted of the patients who participated in the CROSS trial.[2] The CROSS trial, published in 2012, proved convincingly the survival benefit of neoadjuvant CRT, followed by surgery over surgery alone for esophageal cancer [median overall survival of 49.4 months in the CRT surgery group vs 24.0 months in the surgery group; hazard ratio (HR) = 0.657; 95% confidence interval, 0.495–0.871; $P = 0.003$]. This significant survival benefit in CRT surgery groups has been attributed to sterilization of surgical margins (reflected by a higher frequency of R0 resection in the CRT surgery group than in the esophageal cancer. They were of the opinion that this discrepancy can be attributed to sterilization of many initial positive nodes carried out by neoadjuvant CRT.

We believe that this is oversimplification of a complex issue. Although the number of lymph nodes might be more reliable and robust than surgical approach alone for the purpose of statistical analysis, the concept of systematic lymphadenectomy is based on the careful dissection of anatomically well-defined nodal stations.[2] It also needs to be highlighted that the number of resected lymph nodes is a surrogate marker for the quality of lymphadenectomy for the purpose of statistical analysis in view of wide variations in surgical philosophy and practice between institutions and individual surgeons; however, the effect of the surrogate factor (the number of resected lymph nodes) cannot be placed above that of the real factor, that is, surgical diligence in lymph node dissection.

We believe that the issue of stage migration is overstated in the context of extended lymphadenectomy for several cancers. Stage migration (Will-Rogers phenomenon) can possibly explain the stage for stage survival benefit owing to a better staging by a more thorough lymphadenectomy, but it cannot explain the survival benefit of the entire different from each other in terms of oncologic outcome; it is perhaps better to avoid thoracotomy and to adopt a transhiatal approach in such a scenario. The real benefit of the transthoracic approach is the opportunity for a thorough and systematic lymphadenectomy in the mediastinum. This benefit, in our opinion, will continue to hold even after neoadjuvant CRT. Solomon et al[8] reiterated that survival benefit of neoadjuvant therapy and lymphadenectomy is additive as both are independent predictors of improved survival. We believe that the addition of neoadjuvant therapy in esophageal cancer must not be as a compensatory safeguard to disguise the inadequacies of a suboptimal surgery; rather, both these modalities must be additive to maximize the survival benefit.

Durgatosh Pandey, MS, DNB, MCh
Department of Surgical Oncology
All India Institute of Medical Sciences
New Delhi, India

Rambha Pandey, MD
Department of Radiation Oncology
All India Institute of Medical Sciences
New Delhi, India

Pankaj Kumar Garg, MS

surgery-alone group, 92% vs 69%; $P < 0.001$) and sterilization of positive lymph nodes. On the basis of this premise, Talsma et al[1] questioned the applicability of lymphadenectomy in the CRT surgery group.

The authors evaluated the role of lymphadenectomy in both groups—CRT surgery and surgery alone. The authors opined, based on statistical analysis, the number of resected nodes was significantly associated with survival (HR = 0.76 per every 10 additionally resected nodes; $P < 0.01$) in the surgery-alone group; moreover, a positive association exists between the number of resected nodes and the number of resected positive nodes. This conclusion sheds light on the role of adequate lymphadenectomy in esophageal cancer and strengthens its therapeutic potential in addition to its role in better final disease staging. The authors further clarified that the adequate lymphadenectomy failed to provide therapeutic benefit in the CRT surgery group, as the number of resected positive nodes were independent of total resected nodes and so questioned the role of lymphadenectomy in cohort of patients including all stages. An impeccable trial design to address the question of survival benefit (therapeutic potential) of lymphadenectomy in esophageal cancer would be to compare systematic lymphadenectomy versus no lymphadenectomy, head to head, irrespective of the stage (to avoid the confounding effect of stage migration). As we do not have such a randomized trial, the studies focusing on the results of extended lymphadenectomy for esophageal cancer become important sources of data to understand the value of such procedure. Most of the surgical series in esophageal cancer that do not focus on lymph node dissection show 5-year overall survival rates between 20% and 25%. In contrast, Akiyama et al[3] demonstrated a 5-year survival rate of 55% for 3-field lymphadenectomy and 38.3% for 2-field lymphadenectomy. Other studies from Japan[4,5] and lately from the West[6,7] show similar results of extended lymphadenectomy for esophageal cancer.

Finally, the debate between transhiatal and transthoracic esophagectomy is futile unless the transthoracic approach is accompanied by mediastinal lymphadenectomy with a wider periesophageal margin. In the absence of a systematic mediastinal lymphadenectomy, 2 different approaches (transthoracic vs transhiatal) for the same procedure, that is, mobilization of esophagus, are unlikely to be

Department of Surgical Oncology
All India Institute of Medical Sciences
New Delhi, India
durgatosh@gmail.com

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Response to Letter

Reply to Letter: "Neoadjuvant Therapy and Lymphadenectomy in Esophageal Cancer Both Are Essential to Maximize Survival Benefit"

Reply:

We thank Dr Pandey and colleagues for their insightful comments and the opportunity to clarify a number of points from our article.[1] Their main point of criticism is that the number of removed lymph nodes is only a surrogate marker for *systematic* lymphadenectomy. Indeed, we have addressed this issue in the discussion. An *adequate* lymphadenectomy is also determined by the relevance of the removed lymph node stations and hence the surgical approach. One has to remove the relevant lymph nodes to have an impact on survival.

Our study has a strong design because it is based on the CROSS trial.[2] In the CROSS trial, patients were randomized between surgery alone and neoadjuvant chemoradiotherapy (nCRT) plus surgery.

Pandey and colleagues refer to studies with weaker designs. In the study by Solomon et al,[3] the effect of systematic lymphadenectomy was stratified for pathological N-stage (pN0 vs pN+), which carries the potential bias of stage migration. In the studies by Altorki et al[4] and Portale et al,[5] only a small minority underwent neoadjuvant therapy, which is exactly the matter that is at stake. The advantage of the study by Portale et al is that it compared surgical approaches (en bloc vs transhiatal), but the design of the trial was not randomized.

We agree that secondary analyses within a randomized trial can merely generate new hypotheses. We need confirmation from observational studies, and ideally randomized controlled trials, to exclude potential biases such as stage migration. Retrospective analyses on the extent of lymphadenectomy from observational data may have only limited value because various selection biases may play up. Groups probably differ for many more variables (tumor type, diagnostic workup, inclusion and exclusion criteria, etc), besides the extent of lymphadenectomy. A secondary analysis of a randomized controlled trial supplies a higher level of evidence than a retrospective comparison.

In the surgery-alone era, we have previously performed a randomized controlled trial nCRT, followed by a limited transhiatal or extended transthoracic resection. But the current evidence from our study suggests that this impact is less important than that from the surgery-alone era.

A. Koen Talsma, MD
Bas P. L. Wijnhoven, MD, PhD
Department of Surgery
Erasmus-MC Medical Center
Rotterdam, The Netherlands

Ewout W. Steyerberg, PhD
Department of Public Health
Erasmus-MC Medical Center
Rotterdam, The Netherlands

J. Jan B. van Lanschot, MD PhD
Department of Surgery
Erasmus-MC Medical Center
Rotterdam, The Netherlands

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Therefore, we can conclude that after surgery alone a higher number of resected nodes were associated with survival whereas this association was lost in a comparable group of patients who underwent surgery after nCRT. The randomization was stratified for treatment center, clinical N-stage and histology, which makes asymmetry between both treatment arms in, for example, disease extension at baseline, surgical technique or lymph node examination by the pathology department unlikely. Moreover, statistical adjustments excluded these characteristics as an explanation of the observed associations.

comparing transhiatal resection with limited lymphadenectomy versus transthoracic resection with extended lymphadenectomy.[6] The mean number of removed lymph nodes doubled after extended resection (from 16 ± 9 to 31 ± 14 nodes), and there was a nonsignificant trend toward improved long-term survival. In line with this, the present study supports a potential therapeutic benefit of extended lymphadenectomy in the surgery-alone group.

To quantify the therapeutic impact of extended lymphadenectomy for patients after neoadjuvant treatment, we need a randomized controlled trial in which patients receive

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Impact of Neoadjuvant Chemoradiation on Lymph Node Status in Esophageal Cancer: Post hoc Analysis of a Randomized Controlled Trial

To the Editor:

We have read with great interest the recent article by Robb et al in *Annals of Surgery*.[1] The French study group elegantly reanalyzed data of the FFCD 9901 trial.[2] This randomized clinical trial compared survival after neoadjuvant chemoradiotherapy (nCRT) followed by surgery with surgery alone of patients with esophageal squamous cell carcinoma. The authors show that the number of resected lymph nodes and the number of positive nodes identified are reduced after nCRT compared with surgery alone.

Previous studies have shown that maximizing the number of resected nodes is still relevant for improving outcome after nCRT,[3,4] whereas other cohort and population

In our opinion, the assertion made by the authors that their results do not challenge the indication for maximization of lymph node dissection during esophagectomy is, however, debatable. The analysis of the CROSS trial showed 2 important findings: (1) after nCRT, there was no association between the number of resected lymph nodes and survival; this was in sharp contrast to the group of patients in that trial who underwent surgery alone; and (2) after nCRT, there was no association between the total number of resected lymph nodes and the number of positive nodes. In our view these findings suggest that an extended lymphadenectomy is neither necessary for therapeutic nor for prognostic reasons. It would be of great interest if Robb et al could also present their data on the potential association between the number of resected nodes and the number of positive nodes.

Ultimately, to properly address the impact of surgical approach on lymph node retrieval and survival, a new randomized trial should be carried out comparing a transhiatal and transthoracic approach in the era of nCRT, preferably focusing on truly esophageal (Siewert type-1) cancers.[10]

Koen Talsma, MD, MSc
Bas Wijnhoven, MD, PhD
Jan van Lanschot, MD, PhD

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based studies have concluded the opposite.[5–8] The study by Robb et al is the second study using data from a carefully conducted randomized controlled clinical trial and indicates that there is no association between the total number of resected nodes and survival. An earlier *post hoc* analysis of the Dutch randomized CROSS trial published in *Annals of Surgery*[9] showed similar results.

Mark van Berge Henegouwen, MD, PhD
Department of Surgery
Suite H-812, Erasmus Medical Center
Rotterdam, The Netherlands
koentalsma@hotmail.com

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Chapter 6

The 30-day versus in-hospital and 90-day mortality after esophagectomy as indicators for quality of care

A. KOEN TALSMA[1] MD,
HESTER F. LINGSMA PHD[2],
EWOUT W. STEYERBERG PHD[2],
BAS P.L.WIJNHOVEN[1] MD PHD
J. JAN B. VAN LANSCHOT[1] MD PHD

1 Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands
2 Department of Public Health and Medical Decision Making, Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Objective

To describe causes of death in the first year after esophagectomy and determine the time frame that should be used for measurement of quality of surgery. A case-mix adjustment model was developed for the comparison between hospitals.

Summary background data

It is debated over which time period postoperative mortality should be measured as a performance indicator.

Methods

Cause of death was identified for patients in a tertiary referral hospital who died within one year after surgery and classified as surgery related or not surgery related. Sensitivity and specificity for detecting deaths related to surgery were calculated for different periods of follow-up. Case-mix adjustment models for 30DM, IHM and 90DM were developed.

Results

In total 1,282 patients underwent esophagectomy. 30DM was 2.9%, IHM was 5.1% and 90DM was 7%. Beyond 30 days a substantial number of deaths was related to the operation, especially due to anastomotic leakage. Post-discharge non-oncological mortality was most frequently caused by sudden death. One in five patients died because of recurrent disease, being the most important threat in the first year after surgery. The 30DM had a sensitivity for detecting surgery related deaths of 33% and a specificity of 100%. The 90DM had a sensitivity of 74% and a specificity of 96%.

Conclusions

A period of postoperative follow-up longer than 30 days needs to be considered when comparing surgical performance between institutes. In the case mix adjustment model for 90DM, no other variables have to be taken into account compared to those involved in 30DM.

INTRODUCTION

There is an increasing interest in performance indicators as instruments for comparing quality of care between institutions. For surgical procedures postoperative mortality rates are generally used. Currently it is unclear which definition of postoperative mortality best reflects surgical quality of care. Being such a crucial statistic, its definition warrants in-depth consideration. The 30-day operative mortality (30DM) and the in-hospital mortality (IHM) after esophageal resection are well documented and vary from 4% for specialised centers to > 10% for nationwide registries [1, 2]. Few studies report on mortality beyond 30 days. Damhuis et al. however showed in the Dutch Cancer Registry that 43% of in-hospital deaths after surgery for esophageal cancer occurred 30 days or more after the operation [3]. In that study, the reported figures were unadjusted for patient and tumor related characteristics and causes of death were unknown.

Using a longer time period after the operation for defining postoperative mortality may therefore provide a better definition of quality of surgery [4]. Extending the mortality period beyond 30 days has the advantage that patients who die because of surgery related complications outside the hospital are included as well. On the other hand, patients who die because of recurrent disease are also 'erroneously' included at an increased rate as the postoperative period is prolonged. However, it should be underlined that the quality of surgical care in the treatment of esophageal cancer is not reflected by short-term morbidity and mortality only. Good surgical technique with meticulous, radical resection and lymph node dissection will result in better long-term oncological outcome, by some believed to be at the expense of perhaps somewhat worse short term non-oncological results.

From the literature it is unclear how many additional deaths are captured if the time window of postoperative mortality is expanded after 30 days and outside the hospital and whether this is relevant for comparing surgical performance. An exact cut-off value that defines a period of surgery related deaths has not been established. Some authors have suggested 90DM but this is as arbitrary as 30DM and has not been supported by solid data. Little attention has been paid in the literature to the detailed description of causes of death in the first year after esophageal resection.

The aim of the present study was to describe causes of death beyond the traditional 30 days after esophageal resection; (2) to determine which time frame should be used to measure postoperative (non-oncological) mortality as a proxy of quality of surgery for esophageal cancer; and (3) to develop a case-mix adjustment model for comparison of postoperative mortality after esophageal resection between hospitals.

METHODS

Patients who underwent esophagectomy with curative intent for carcinoma of the esophagus or esophago-gastric junction (EGJ; Siewert type 1 and 2) between January 1991 and

October 2011 were identified from a prospectively collected database. This cohort represents patients at the Erasmus MC University Medical Center (Rotterdam, the Netherlands), a tertiary referral and high-volume hospital. Excluded were patients who underwent an exploratory laparotomy/thoracotomy, additional organ resections (other than spleen) and a follow-up time less than 365 days.

All patients underwent a standard diagnostic work-up including endoscopy with histological biopsies, endoscopic ultrasound (EUS), CT-scan of chest and abdomen and external ultrasonography of the neck. A PET scan was not routinely performed during the study period. Some patients received neoadjuvant chemo(radio)therapy in the context of randomised controlled trials [2, 5]. In some cases, induction chemoradiotherapy or chemotherapy was given to patients with either a cT4-tumor without distant metastases or in patients with gross involvement of coeliac trunk lymph nodes who were not considered elegible for primary surgical therapy. The pathological staging of the tumor was based on the 7th edition of the TNM staging system [6]. Cardiovascular comorbidity was defined as a history of ischaemic heart disease, abnormal electrocardiogram findings or a diminished left ventricular ejection fraction. Pulmonary comorbidity was defined as a history of chronic pulmonary disease. Substantial preoperative weight loss was defined as loss exceeding 10% within 6 months before surgery. Esophagectomy was performed through a transhiatal or transthoracic surgical approach. Both techniques have been described elsewhere [7].

Definition of outcome measures

The primary outcome measure for this study was postoperative mortality. This was defined as 30-day mortality (30DM), in-hospital mortality (IHM) and 90-day mortality (90DM). Thirty- and 90-day mortality were defined as death within 30 or 90 days respectively after date of surgery, and in-hospital mortality was defined as death at any time during the postoperative hospital stay. Deaths were counted as having occurred after discharge if patients survived the first hospital admission, including patients that were transported to a different hospital. Death during re-admission was counted as having occurred out of hospital, because it happened after the index admission. After discharge, surviving patients were followed at regular intervals at the outpatient clinic until five years after the operation. Last follow-up checkpoint was November 1st 2012.

Causes of death

The methodology of Waljee et al. [8] was used for classifying systematically and reliably the 'seminal' cause of death in all patients who died within one year after surgery. One reviewer (AKT; corresponding author), after having identified in the medical files all complications that occurred during a patient's postoperative course, chose the complication that most contributed to the patient's death. In case of doubt, the patient's history was discussed with one of the surgical co-authors (BPLW or JJBvL). Patients with a radiologically or pathologically proven recurrence of disease were counted as having died because of an oncological reason. Patients who died due to worsening clinical performance without a radiologically or

pathologically proven recurrence of disease were counted in the category “Failure to thrive”. General practitioners were contacted if cause of death could not be determined from the patients’ paper and electronic files. Death certificates from the Central Bureau of Statistics were not used. The seminal complication is defined as the first event leading to the chain of subsequent complications that culminated in a patient’s death. Based on clinical relevance and frequency of occurrence, fatal events were identified and categorised into nine of the following entities: 1. anastomotic leakage with sepsis (incl. mediastinitis and esophago-tracheal fistula); 2. progression of disease (due to either systemic or locoregional recurrence); 3. pneumonia or any other pulmonary event (aspiration, acute respiratory distress syndrome etc.); 4. failure to wean from mechanical ventilation; 5. sudden death (at home or during admission without prodromal symptoms e.g. myocardial infarction, pulmonary embolus); 6. peroperative complication (haemorrhage, stroke, myocardial infarction); 7. medical complication other than pneumonia (stroke, renal failure, hepatic failure); 8. failure to thrive without evidence of progressive disease; or 9. abdominal sepis (not related to 1., e.g. diverticulitis, pancreatitis). Based on these descriptions, the seminal cause of death for each patient was grouped in two broad categories: (in)directly surgically or medically related to the operation versus recurrence of disease. Surgical complications included: Anastomotic leakage / mediastinitis, Per-/intraoperative surgical complications (hemorrhage) and Abdominal sepsis. Medical complications included (Aspiration) Pneumonia or other pulmonary event, Failure to wean, Sudden death, Per-/intraoperative non-surgical complications (stroke, cardiac), Stroke, Renal failure, Failure to thrive. Oncological reasons of death included: Progression/recurrence of disease (locoregional recurrence, distant metastases). Patients who died after worsening clinical performance without a radiologically or pathologically proven recurrence of disease were counted in the category “Failure to thrive”. Patients with gross recurrence of disease were counted as having died because of progression of disease. Patients with minimal recurrence who died because of an intercurrent event were counted as having died because of that event.

Statistical analysis

Postoperative death was used as the outcome variable. Multiple imputation was performed for missing predictor values. To determine which timeframe would include the maximal percentage of deaths related to surgery and would exclude the maximal percentage of deaths due to recurrent disease, sensitivity and specificity were calculated for different periods of follow-up and a ROC curve was drawn. Logistic regression models were used to determine risk factors for the following outcomes as dependent variables: 30DM, IHM, and 90DM. Non-linearity was assessed for continuous predictors, such as age. Variables with a p-value < 0.15 in the univariable model were considered to be possible independent predictors and subsequently entered into the multivariable model. Two-tailed $p<0.05$ was considered statistically significant. All analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL, USA) and R (R statistical software , Vienna, Austria).

RESULTS

Clinicopathological characteristics

Between January 1991 and October 2011, 1,286 patients underwent esophageal resection for carcinoma. Three patients were excluded because of additional resections (pulmonary wedge, wide local excision of GIST in gastric tube). One patient was excluded because of loss to follow up. The clinical characteristics of the resulting 1,282 patients in the cohort are shown in Table 1. Median age was 63 years and most of the patients were male. Median length of stay in the hospital was 15 days. The majority of patients had advanced disease (pT3-4 and/or lymph node metastases). Most esophagectomies (71.5%) were done for adenocarcinomas of the distal esophagus or EGJ. Transhiatal resection with gastric tube reconstruction was the preferred surgical approach, especially in the earlier parts of the study period. A minority had significant medical comorbidity. One patient was excluded from regression analysis, because the tumor was not taken out due to a fatal myocardial infarction during surgery.

Definiton dependent mortality

The 30DM, IHM and 90DM rates of patients were 2.9%, 5.1% and 7.0% respectively (Figure 1). Overall, 53 deaths (4.1%) occurred between 30 and 90 days postoperatively and 29% of the total cohort did not survive the first year after surgery. The unadjusted mortality rates did not significantly change during the study period (data not shown).

Causes of death

For all patients who died in the hospital as well as for most patients who died after discharge, the single most important event that lead to death could be derived from the medical files. In all other cases, the general practitioner was contacted. For 15 patients, we contacted family members to evaluate the clinical condition of these patients in the weeks before death. For five patients we could not by all means identify cause of death.

The distribution and causes of deaths by time period and moment of discharge are shown in Table 2 and Supplementary Figure 1. Of the 37 patients who died within 30 days after surgery, the most common cause was anastomotic leakage or sudden death. However, anastomotic leakage could still result in a fatal outcome after 30 days as well. Esophago-tracheal fistula as a manifestation of anastomotic leakage was fatal in almost all cases. There were ten patients who died between 30 and 90 days after surgery because of recurrent disease, all with haematogenous metastases that had not been detected during primary diagnostic work-up. After 90 days, cancer related death was heavily dominating with one in five patients dying due to progression of disease during the first year. Development of respiratory failure occurred in the majority of all septic fatal complications, but pneumonia and failure to wean were identified as the seminal complication leading to death in 22 patients. Most patients who could not be weaned from the ventilator survived longer than 30 days, but not beyond 90 days. In 14 of the 24 patients who died because of ‘sudden death’, this

happened after discharge. Five patients died of a complication during surgery, two among these because of fatal intraoperative haemorrhage, the source of bleeding being the aorta in both cases. Other causes of death that were encountered were stroke, renal failure and failure to thrive. This last group of patients with failure to thrive deceased in nursery homes. Abdominal sepsis (leakage of jejunal feeding tube, diverticulitis and pancreatitis) contributed to in-hospital mortality in 7 patients. Only fifteen of the 71 patients who died in the hospital were autopsied.

ROC analysis

The distribution of causes of death over time after surgery is shown graphically in Figure 2. To determine which timeframe would include the maximal percentage of deaths related to surgery and would exclude the maximal percentage of deaths due to recurrence, sensitivity and specificity were calculated for different periods of follow-up (Figure 3). For deaths medically or technically related to surgery (surgical deaths), 33% would be captured at 30 days, whereas 74% would be captured at 90 days. Note from the resulting ROC curve in Figure 3 that in this study the time point of 105 days after surgery is the threshold that is found when the sum of sensitivity and specificity are maximized (sensitivity 79% and specificity 94 %).

Case mix adjustment models

In the univariable analysis it was found that age, gender, tumor location, surgical approach, reconstruction type, resection margin involvement, history of cardiovascular disease and substantial preoperative weight loss were significant predictors of both 30-day and 90-day mortality. For age, the odds ratio (OR) for every year increment after 60 years was calculated, because the effect was non-linear before that age. For 30-day mortality there was a trend for additional variables (i.e. neoadjuvant therapy, history of pulmonary disease, diabetes or stroke/TIA) which reached significance for 90-day mortality. Transhiatal esophagectomy was associated with a lower 90DM rate compared to a transthoracic surgical approach (6.0% and 9.7% respectively). In univariable analysis for IHM the following variables were significantly associated: age, gender, neoadjuvant therapy, surgical approach, reconstruction type and history of cardiovascular or pulmonary disease or stroke/TIA. Year of operation was not univariably associated to survival for any of these short term outcomes. Stratified analysis of 30DM, IHM and 90DM by multivariable logistic regressions and the resulting case-mix adjusted models are summarized in Table 3. To identify risk factors for death after discharge, logistic regression was also conducted using death after discharge due to a surgically related cause as the dependent variable. This showed that patients with advanced age, positive resection margin and longer hospital stay are at an increased risk of dying early after discharge (data not shown).

DISCUSSION

In this study 30DM, IHM and 90DM rates were investigated in a large cohort of patients who underwent esophagectomy at a high-volume tertiary referral center. It confirmed the earlier finding that 30DM does not completely reflect the postoperative mortality risk. A substantial number of patients died beyond 30 days of surgery: 30DM was 2.7 % and 90DM 7.0 %. The definition of IHM has often been criticized for being dependent on length of stay and discharge practices, but has the advantage that it includes fatal complications that can be treated temporarily and beyond 30 or 90 days. A composite measure of both IHM and 90DM, that is traditionally used in the US provides a more complete picture and was 7.4% in the present study.

In the present study we were able to identify and further categorize cause of death for almost every patient in the first year after surgery and, therefore, to determine whether death was due to surgical or medical complications of the operation versus death due to recurrence/progression of cancer. A substantial number of deaths between 30 and 90 days after surgery were due to complications related to surgery with anastomotic complications and sudden death being the most frequent causes. Extending the follow-up beyond 90 days after surgery resulted mainly in the inclusion of more patients who died of recurrent disease as opposed to medical or technical complications related to surgery. This was not different for to two surgical approaches. Esophageal cancer surgeons should realize that they have to compare both the short term and the long term outcomes of their patients with the benchmark as both aspects are relevant for comparing surgical performance. Both surgery related deaths and cancer recurrence related deaths are reflections of surgical quality of care. Less radical surgical resections will generally result in lower postoperative morbidity and mortality, but will give less favourable oncological outcomes. The ROC curve shown in this study can be used to select an optimal threshold balancing the inherent tradeoffs that exist between sensitivity and sensitivity for surgery related deaths for all possible follow up periods. Depending on the focus (e.g. surgical safety or oncological performance and patient selection), one has to choose between evaluating the optimal threshold by maximizing the sum of sensitivity and specificity or give different weights to sensitivity and specificity. In this study ROC analysis showed that postoperative day 105 after surgery was the time point that best discriminated between surgery related deaths and cancer recurrence related deaths.

From an oncological point of view, 1-year survival rate provides more useful data than immediate postoperative mortality [4]. In the present data, 1-year survival rate was only 71% suggesting that apart from more effective neoadjuvant therapy and more radical resection further refinement is required in the selection of patients who will sufficiently benefit from potentially curative but aggressive surgery.

Respiratory failure is a major problem after esophagectomy. Several studies have reported that about half of the in-hospital deaths after esophagectomy is due to pneumonia [9-11]. Although some kind of respiratory failure was present in almost all fatal events in the present study, pulmonary complications were the direct, 'seminal' cause of death in one

in four patients who died in the hospital. In the present study, more fatal pulmonary events (including impossibility to wean from mechanical ventilator) occurred in patients who underwent a transthoracic surgical approach compared to those who underwent a transhiatal approach (33.4 % of all deaths before 90 days after a transthoracic approach were due to pulmonary complications versus 10.8 % of deaths after transhiatal approach). The percentage of deaths due to fatal anastomotic leakage or sudden death was not different for the two approaches. Also of interest is the group of patients who died at home because of a sudden death. It would be interesting to subdivide these causes into cardiac events and pulmonary embolisms, but unfortunately in the great majority no autopsy reports were available. In a separate analysis it was found that patients with advanced age, positive resection margins and longer length of hospital stay are at an increased risk of suddenly dying after discharge, perhaps suggesting that at least some of these patients might have benefitted from prolonged thromboprophylaxis.

Even after agreement on a uniform definition of postoperative mortality, direct comparison of crude mortality rates between hospitals can be misleading as they do not take into account the case-mix difference, i.e. the differences in physiological condition and tumor stages of patients. Sophisticated models have been developed for prediction of 30DM [12, 13] and IHM11, [14-17] after esophageal surgery, but models for 90DM have been mostly based on large multi-institutional databases with only few parameters available [18]. In the present study a large number of prospectively collected variables were available to construct a model for 90DM that allows individual centers to compare their results with others as a means towards quality improvement. Age, gender, surgical approach, resection margin involvement, history of cardiovascular disease and substantial preoperative weight loss were independent predictive factors for death within 90 days after esophagectomy. Interestingly, in 90DM the same predictors were involved as in 30DM, confirming our previous research [15, 16]. In patients older than 75 years of age, the 90-day mortality rate was 17.1%. In previous publications, some authors claim that such extensive surgery ought to be considered very carefully in this high age group [13, 19]. With respect to surgical approach it has been shown previously that there is a 5-year survival benefit for the transthoracic technique in some patients [7, 20]. In the multicenter trial comparing surgical approaches, mortality was 4 % aftrer transthoracic resection and 2 % after transhiatal resection, but this difference was not statistically significant. In the present study that included 1,282 patients, the twofold increased risk of dying was statistically significant. Moreover, in the present observational study a selection bias might play a role because patients with larger tumors might more frequently have undergone a transthoracic surgical approach. Incomplete resection as a risk factor for 30DM, IHM and 90DM is probably a reflection of high tumor load and more extensive and aggressive surgery. Of the patients who died within 90 days after surgery in this study, 40% underwent an irradical resection. This was reported in a Japanese study as well [11]. The present study reproduced the finding of previous authors that substantial preoperative weight loss is associated with increased mortality and early recurrence [12,

21, 22]. Some previous reports suggest higher morbidity [23] for patients after chemo(radio) therapy, while others do not [24]. Only a randomized controlled trial can cancel out the validity issues of 'confounding by indication' that occurs in observational studies like the present study. There have been various reasons for the administration of preoperative therapy in this study population. Some patients received neoadjuvant chemotherapy [5] or neoadjuvant chemoradiotherapy [2] in the context of RCTs, thus excluding selection bias. Other patients received induction chemotherapy outside RCTs because of advanced tumors which were considered inoperable at first presentation and would only proceed to surgery in case of a favourable tumor response. In that subgroup of patients a selection bias was introduced, with relatively unfavourable patients receiving induction therapy. It has been repeatedly shown that esophageal cancers which are insensitive to neoadjuvant therapy are associated with poor survival. Unfortunately, there were too many missing values in the present study to analyze the potential relation between tumor regression grade and (timing of) cancer death.

The present study has some limitations, including the retrospective accumulation and addition of some variables to our prospectively collected database. The cause of sudden death was unknown in some of the late mortalities. The strength of the study, on the other hand, was the limited number of missing data on cause of death, for example unequivocally due to surgery or cancer progression. The results presented in this study are from a single institution and thus may not be broadly applicable. The mortality rates reported can vary with other reports in high volume centers for the reason that short-term outcome event rates are relatively low. This shows, besides issues of definition and case-mix correction, another element of complexity in comparing surgical performance, i.e the problem of sample size [25].

In conclusion, this study shows that patients undergoing esophagectomy for cancer continue to have a surgery associated mortality risk after 30 days and after discharge, with anastomotic leakage and sudden death being the most frequent causes of death. The case-mix factors associated with 90DM do not differ significantly from those involved in 30DM. Future studies should investigate if these findings have implications for ranking hospital performance by using data on both mortality definitions. Despite careful preoperative selection, the most severe threat for esophageal cancer patients in the first year after potentially curative surgery is still cancer recurrence. It would be helpful if hospital performance in esophageal surgery would include 90DM along with 1-year survival reflecting the quality of both the diagnostic and the therapeutic process.

Table 1
Clinico-pathological characteristics of 1,282 patients who underwent surgical resection for esophageal or EG junctional carcinoma.

Age [yrs]		**63 (19-89)**
Gender	Male Female	**988 (77)** **294 (23)**
Length of hospital stay [days]		**15 (0-186)**
Tumor category [pathology]	ypT0 or no residu after endoscopic resection HGD*, Tis or T1 T2 T3 T4	**96 (7.5)** **229 (17.8)** **197 (15.4)** **746 (58.1)** **13 (1.0)**
Node category based on TNM7**	N0 N1 N2 N3	**623 (48.6)** **352 (27.4)** **187 (14.6)** **119 (9.3)**
Tumor type	Squamous cell carcinoma Adenocarcinoma Undifferentiated	**349 (27.3)** **917 (71.5)** **16 (1.2)**
Grade of differentiation	Good Moderate Poor Unknown	**128 (10.0)** **566 (44.2)** **545 (42.5)** **43 (3.4)**
Tumour location	Proximal 1/3 Middle 1/3 Lower 1/3 Esophagogastric junction	**21 (1.6)** **161 (12.6)** **554 (43.2)** **546 (42.6)**
Neoadjuvant therapy		**468 (36.5)**

Surgical approach	Transhiatal Transthoracic	**941 (73.3)** **341 (26.7)**
Reconstruction type	Gastric tube Colonic interposition No reconstruction	**1237 (96.5)** **40 (3.1)** **5 (0.4)**
Resection margin involvement***	R0 R1,R2 (any margin)	**960 (74.8)** **321 (25.0)**
Co-morbidity	Cardiovascular disease Pulmonary disease Diabetes Stroke/TIA****	**290 (22.6)** **117 (13.8)** **106 (8.3)** **66 (5.1)**
Weight loss >10% prior to surgery	Yes Unknown	**763 (59.5)** **15 (1.2)**
Period of surgery 1991-1995 1996-2000 2001-2005 2006-2011		 **266** **283** **360** **373**

data shown are mean (SD) or median (range) or number (prevalence percentage); the sum of numbers may not equal 1282 because in one patient the tumour was not taken out. *HGD = hidh grade Dysplasia; ** Node category according to 7th edition TNM-staging system: N0 (no positive nodes), N1 (1-2 positive nodes), N2 (3-6 positive nodes) and N3 (>6 positive nodes); *** R0=resection margin microscopically tumor-free, >1mm; R1=resection margin microscopically <1mm; R2=macroscopically residual tumor; ****TIA = transient ischaemic attack.

Table 2
The distribution and causes of death by time period and moment of discharge

Causes of death	30DM		30-90DM		90-365DM		1-5 yr M
	In-hospital	After discharge	In-hospital	After discharge	In-hospital	After discharge	
Etiology of death							
Surgically related to operation	15	1	17	1	4	8	
Medically related to operation	18	2	13	12		16	
Oncological	0		2	8	1	249	355
Unknown		1				4	55
Description							
Anastomotic leakage / mediastinitis	11	1	14	1	2	6*	
Progression of disease			2	8		249	355
(Aspiration) pneumonia or other pulmonary event	5		4	1	1	4	
Failure to wean	1		6				
Sudden death e.g. myocardial infarction, pulmonary embolism	9	2	1	5		7	
Peroperative complication surgical bleeding medical, stroke, cardiac failure	2 2 1					1*	
Medical complication other than pneumonia e.g. stroke, renal failure	1		2	3		5	
Failure to thrive without evidence of progressive disease (nursery home)				2			
Abdominal sepis	2		3	1	2	1*	
Total	34	3	32	21	5	277	410
Cumulative Mortality Rate	37/1282=2.9%		90/1282=7.0%		372/1282=29%		782/1282=61%

* including fatal complications secondary to reconstruction surgery after cervical oesophageal deviation

Table 3
Odds Ratios (95%CI) for Multivariable predictors of mortality by definition

	Category	Reference	Odds Ratio for 30DM	Odds Ratio for IHM	Odds Ratio for 90DM
Age	Every increase in age by year above 60		1.09 (1.03-1.12) *	1.10 (1.05-1.12)*	1.10 (1.04-1.09)*
Gender	Female	Male	0.29 (0.06-0.74) *	0.51 (0.31-0.95)*	0.49 (0.27-0.93)*
Neoadjuvant Therapy	Yes	No		0.72 (0.40-1.28)	0.69 (0.39-1.14)
Surgical Approach	TTE	THE	2.13 (1.04-4.64) *	2.30 (1.26-3.85)*	2.04 (1.34-3.70)*
Reconstruction type	Colonic interposition	Gastric tube	2.6 (0.74-10.09)	2.0 (0.66-6.39)	1.75 (0.71-5.59)
Resection Margin	R1 or R2	R0	2.5 (1.20-4.79) *		1.59 (0.97-2.55)
Comorbidity					
Cardiovascular disease	Yes	No	1.60 (0.84-3.58)	1.56 (0.97-2.76)	1.60 (1.06-2.82)*
Pulmonary disease	Yes	No		1.82 (1.08-3.44)*	1.10 (0.62-2.06)
Diabetes	Yes	No			1.14 (0.57-2.32)
Stroke/TIA	Yes	No		1.37 (0.61-3.41)	1.13 (0.57-2.97)
Substantial weight Loss	Yes	No	2.1 (0.95-4.57)		1.71 (1.02-2.72)*

30DM = 30-day mortality; IHM = in-hospital mortality; 90DM = 90-day mortality; TTE = transthoracic esophagectomy; THE = transhiatal esophagectomy; TIA = transient ischemic attack; * p-value <0.05

Figure 1
30-, 90-, 365-day and in-hospital mortality rates (%) in a cohort of 1,282 patients who underwent esophageal cancer resection

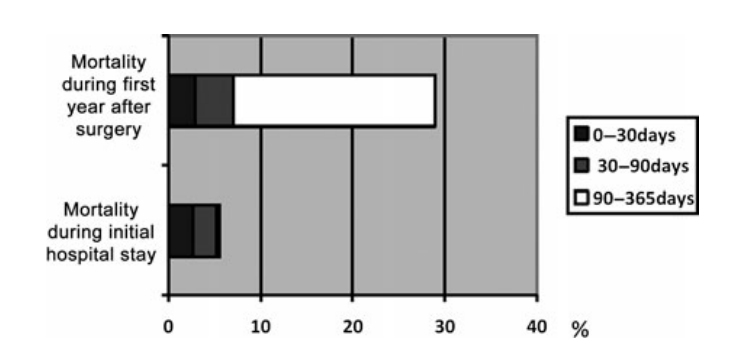


Figure 2
The distribution of causes of death over time after surgery

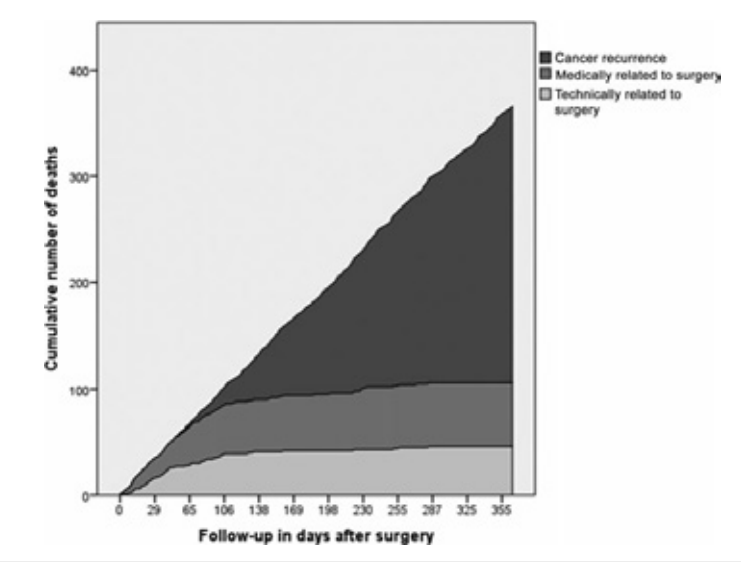
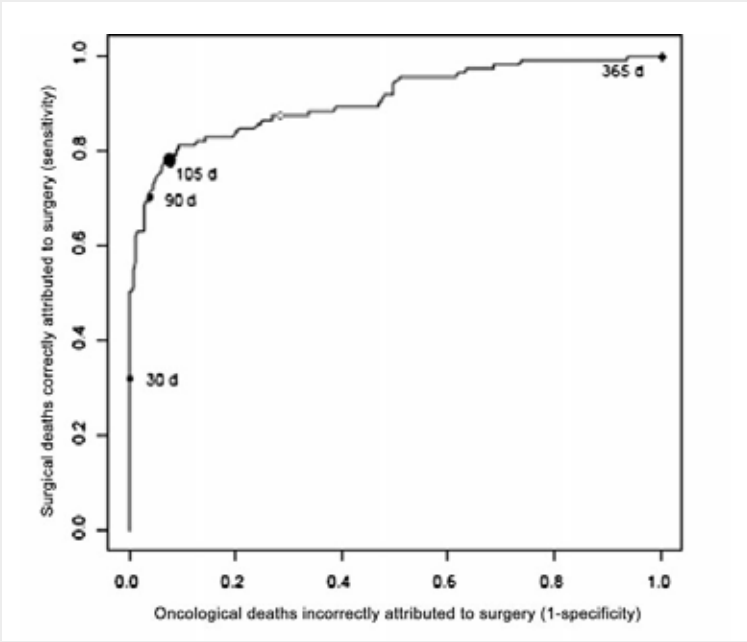


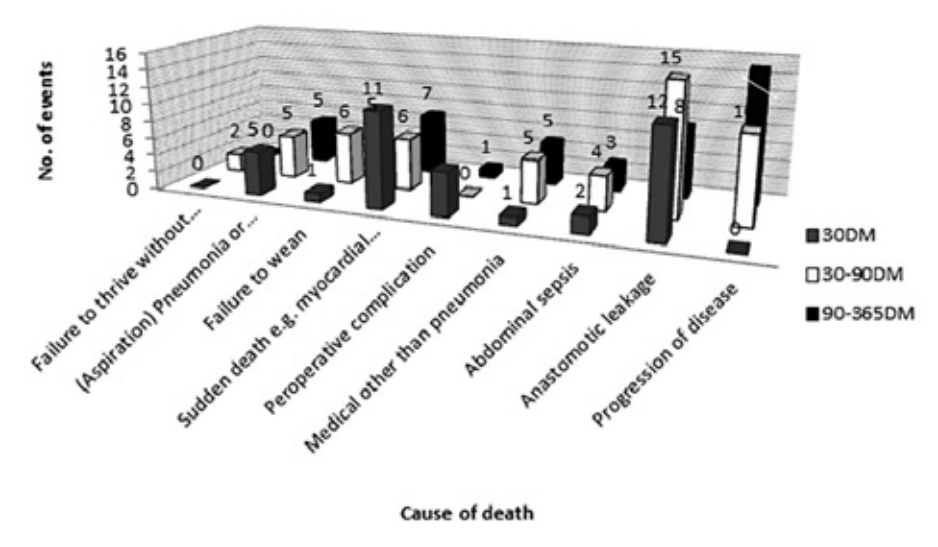
Figure 3
Receiver Operating Characteristic (ROC) Curve for detection of surgery related deaths calculated for different time frames after surgery.



Time frame	Missed surgery related deaths (FN*)	Included oncological deaths (FP)	Sensitivity (=TP/ TP+FN)	Specificity (=TN/ FP + TN)
30 days	71	0	33%	100%
90 days	28	10	74%	96%
105 days	23	16	79%	94%

*FN indicates false negative; FP, false positive; TP, true positive; TN, true negative.

Supplementary Figure 1
The distribution and causes of death by time period



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Chapter 7

Determinants of improved survival after oesophagectomy for cancer

A. K. TALSMA[1],
R. A. M. DAMHUIS[3],
E. W. STEYERBERG[2],
C. ROSMAN[4],
J. J. B. VAN LANSCHOT[1],
B. P. L. WIJNHOVEN[1]

Departments of
1 Surgery and
2 Public Health, Erasmus MC – University Medical Centre Rotterdam, Rotterdam,
3 Department of Registry and Research, Comprehensive Cancer Centre the Netherlands, Utrecht, and
4 Department of Surgery, Canisius Hospital, Nijmegen, The Netherlands

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ABSTRACT

Background

Survival after oesophagectomy for cancer seems to be improving. This study aimed to identify the most important contributors to this change.

Methods

Patients who underwent oesophagectomy from 1999 to 2010 were extracted from the Netherlands Cancer Registry. Four time periods were compared: 1999–2001 (period 1), 2002–2004 (period 2), 2005–2007 (period 3) and 2008-2010 (period 4). Hospital type, tumour location, tumour type, tumour differentiation, neoadjuvant therapy, operation type, (y)pT category, involvement of surgical resection margins, number of removed lymph nodes and number of involved lymph nodes were investigated in relation to trends in survival using multivariable analysis.

Results

A total of 4382 patients were identified. Two-year overall survival rates improved from 49.3 per cent in period 1 to 58.4, 56.2 and 61.0 per cent in periods 2, 3 and 4 respectively ($P < 0.001$). Multivariable survival analysis revealed that the improvement in survival between periods 3 and 4 was related to the introduction of neoadjuvant therapy. The improvement in survival between periods 1 and 2 could not completely be explained by the factors studied. The number of examined lymph nodes increased, especially between periods 2 and 3, but this increase was not associated with the improvement in survival.

Conclusion

The observed increase in long-term survival after surgery for oesophageal cancer between 1999 and 2010 in the Netherlands is difficult to explain fully, although the recent increase seems to be partly attributable to the introduction of neoadjuvant therapy.

INTRODUCTION

A rising incidence in oesophageal cancer is largely explained by increased numbers of adenocarcinomas [1–4]. A population-based study in the Netherlands recently reported an increase in long-term survival after surgery for oesophageal cancer [3]. Many factors might be responsible for this improvement including surgical approach [5,6], introduction of multimodal treatment including chemotherapy and chemoradiotherapy (CRT) [7–9], and better perioperative care [10]. The extent of surgical lymphadenectomy may also be important, as the number of removed lymph nodes can be considered as an indicator of surgical performance, given its association with overall survival [11]. Improved survival might also be due to more favourable patient and tumour characteristics, including the impact of endoscopic surveillance for Barrett's oesophagus and increased public awareness of disease. Novel clinical staging modalities (such as PET) and the introduction of specialist multidisciplinary teams are thought to have improved selection of patients for curative surgery [12]. Centralization of oesophageal surgery in specialized units in the Netherlands also took place in the past 10 years, influencing many of the above issues [13].

Although each of these factors has been investigated in relation to survival after oesophagectomy, the impact of combination of these improvements on survival at a population-based level is largely unknown. The aim of the present study was to identify patient, tumour and treatment characteristics contributing to the observed trend for increased survival after oesophagectomy for cancer in the Netherlands. It was hypothesized at the outset that neoadjuvant CRT and better-quality surgery (as demonstrated by higher lymph node yields) would be the main factors responsible for this improvement.

METHODS

The Netherlands Cancer Registry (NCR) collects data on all patients diagnosed with cancer in the Netherlands, based on notification of all newly diagnosed malignancies by the national automated pathological archive and of additional hospital discharge diagnoses. Completeness is estimated to be at least 95 per cent [14]. For the present study, patients who underwent oesophagectomy for primary oesophageal cancer without evidence of distant metastases between 1999 and 2010 (ICD-O code C15) were identified. Because the present study focused only on patients who underwent an oesophagectomy, and type of surgery and surgical approach were not yet registered routinely during the first half of the study, cardia tumours were excluded to make sure that patients who underwent gastrectomy were not included. Patients with cervical oesophageal tumours that constitute a distinct clinical entity with a different surgical technique and those who received neoadjuvant radiotherapy alone were also excluded.

Information on diagnosis, staging and treatment was extracted routinely from the medical records by specially trained administrators of the NCR. Stage distribution was revised

to the seventh edition of the TNM system of the International Union Against Cancer (UICC) [15]. Tumour location was categorized as follows: lower oesophagus and oesophagogastric junction (C15.5), middle oesophagus (C15.4) or unspecified (C15.8, C15.9). Tumour, institution and patient-related characteristics included age, sex, date of diagnosis, type hospital in which surgery was performed, tumour location, tumour type, tumour differentiation, neoadjuvant therapy, operation type, (y)pT category, involvement of surgical resection margins, number of removed lymph nodes and number of involved lymph nodes. Because of confidentiality regulations, information regarding hospitals was available only at an aggregated level. University hospitals are defined as hospitals affiliated with a teaching and research institution. Hospital type was defined by the hospital of diagnosis before 2005, and by the hospital of surgery thereafter. In the early years of the study some variables (hospital type, operation type, involvement of surgical resection margins) were not registered routinely by all regional data centres. In these instances variables were scored as 'missing'. During statistical testing for time trends, these missing values were excluded from the analysis, with no imputation. Any results that could not be ascertained from the pathology reports or medical records were marked as 'not specified'. Vital status was obtained by annual computerized linkage with the automated national civil registry and included information up to 1 December 2012.

Statistical analysis

The study was divided into four intervals of 3 years: 1999–2001 (period 1), 2002–2004 (period 2), 2005–2007 (period 3) and 2008–2010 (period 4). Differences in patient, tumour and treatment characteristics between the time periods were tested using a t test or Kruskal–Wallis test for continuous variables or by means of a X2 test for proportions. Overall survival was defined as the time interval between date of diagnosis and date of death (event) or 1 December 2012 (censored). Owing to privacy regulations, the specific date of surgery was not available to the investigators and postoperative mortality could not be reported. Survival curves for the four intervals were calculated by the Kaplan–Meier method and compared by log rank test. Because follow-up data were available only until December 2012, 5-year follow-up was not feasible for period 4 and so 2-year survival rates are reported. Of the patients diagnosed in the period 2008–2010 who were alive at the census date, 40.8 per cent had less than 2 years of follow-up.

Unadjusted and adjusted hazard ratios (HRs) were compared between the four periods using Cox analysis, with 1999–2001 as the reference category. In the adjusted analysis, adjustment was made for each variable found to be associated with time. When specific variables directed the adjusted HRs towards 1, this explained (part of) the time trend for improved survival. The change in X2 value for the variable 'period of surgery' (representing how much predictive information the variable gained or lost after adjustment) was compared between unadjusted and adjusted models. A final model consisted of all variables that were identified as significant predictors from a stepwise Cox regression model, in which the variables with least significant P values were dropped at each step, stopping when all values

were significant, defined by a threshold P value of 0.050. Because of co-linearity between the variables neoadjuvant therapy, tumour differentiation, (y)pT category and involvement of surgical resection margins, only neoadjuvant therapy was used in the final model. All analyses were carried out using SPSS® version 19.0 (IBM, Armonk, New York, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From 1999 until 2010, 4756 patients were identified from the NCR. After exclusion of 87 patients with proximal oesophageal tumours and 287 who had neoadjuvant radiotherapy alone, 4382 patients were included in the study. The number of oesophagectomies increased from 793 in period 1 to 1373 in period 4, mainly in non-university teaching hospitals (Table 1). Age and sex distributions remained stable over time. The use of neoadjuvant CRT increased from 2008, meaning that tumour differentiation could not always be reported for patients in period 4. At the beginning of the study, the preferred surgical approach was transhiatal oesophagectomy, whereas by the end one-half of the patients underwent a transthoracic surgical approach. The percentage of patients with tumour-positive surgical resection margins decreased with time from 15.9 per cent in period 1 to 10.0 per cent in period 4. The median number of removed nodes increased from 8 in period 1 to 15 in period 4, but especially between periods 2 and 3, and a higher proportion of patients was diagnosed with node-negative disease ((y)pN0; 40.9 per cent in period 1 and 53.7 per cent in period 4).

Associations between patient, tumour and treatment characteristics and survival

Median follow-up of censored patients was 48 months. Six-month mortality (death within 6 months after date of diagnosis) for periods 1 to 4 was 12.8, 9.3, 7.5 and 6.1 per cent, respectively (Table S1, supporting information). The 2-year survival rate improved from 49.3 per cent in period 1 to 58.4, 56.2 and 61.0 per cent in periods 2, 3 and 4 respectively ($P < 0.001$) (Fig. 1 and Table 2). Younger age and female sex were associated with improved survival. Univariable estimates for survival also showed improved survival for patients who underwent surgery in a university hospital (5-year survival rate 38.5 per cent) compared with non-university teaching hospitals (30.2 per cent; $P < 0.001$) and non-teaching hospitals (23.4 per cent; $P < 0.001$). Tumour type, tumour location and surgical approach were not related to survival. An increased number of removed nodes was associated with better outcome, but this improvement was largely confined to the group of patients with at least 19 removed lymph nodes. Number of involved lymph nodes was associated with survival; there were almost no survivors if more than three positive nodes were identified.

Relative contributors to improved survival

Unadjusted Cox proportional hazards analysis showed a significant improvement in survival between periods 1 and 2 (HR 1.00 versus 0.85; $P < 0.001$), and between periods 3 and 4

(HR 0.86 versus 0.71; P < 0.001) (Table 3). These improvements remained after adjusting for hospital type, number of removed nodes, tumour differentiation, tumour type and number of involved nodes. However, when adjustment was made for neoadjuvant therapy, there was no longer a significant improvement in survival improvement between periods 3 and 4 (model 4; HR 0.86 versus 0.80; P = 0.117). Neoadjuvant therapy accounted for more than half of the improvement in survival between the two latter periods (X2 value decreased from 34 to 15) (Table 3). In the final model, period 4 was no longer associated with improved survival, indicating that the combined variables (age, sex, time period of surgery, hospital type, neoadjuvant therapy, number of removed nodes and number of involved nodes) could negate the improvement in survival in the final period (HR 0.71 in model 1 versus 0.91 in final model), whereas these variables were not able to fully explain the improvement in survival from period 1 to period 2 (HR 0.86 in model 1 versus 0.85 in the final model) (Table 3).

DISCUSSION

The present population-based study shows that long-term survival rates after oesophagectomy for cancer have improved substantially in the past decade. The factors explaining this trend were investigated by adjusting for possible changes in tumour histology and differentiation, patient demographics, and changes in surgical and medical treatment.

It was difficult to dissect out the contribution of the different variables separately given the changes in treatment strategies and epidemiology that have occurred simultaneously. Nevertheless, the increased use of neoadjuvant therapy explained almost half of the improved survival observed in the study period, especially between period 3 (2005–2007) and period 4 (2008–2010). Different neoadjuvant treatment regimens were used during the study period, including chemotherapy, which was popularized in the earlier years [8]. From 2004 to 2008, a large Dutch multicentre trial [9] showed an absolute survival benefit of 13 per cent at 5 years in patients who underwent preoperative CRT; although the final results of this trial were published in 2012, neoadjuvant therapy had already been implemented at a nationwide level from 2008 onwards, as demonstrated in Table 1. The present results mirror the findings of this randomized trial, with an absolute improvement in 5-year survival of 14 per cent in patients who underwent neoadjuvant CRT (Table 2) and an R0 resection rate of 87 per cent (data not shown). After neoadjuvant CRT no viable tumour cells could be identified in the pathology specimen in 203 (25.4 per cent) of 799 patients.

The number of surgical resections almost doubled during the study interval. This probably reflected the rising incidence in adenocarcinoma, but does not easily explain the improved long-term survival, as tumour type was not related to survival in the present study; this is different from previous findings [16,17], but similar to the results of a recent Surveillance, Epidemiology, and End Results (SEER) analysis [18]. Time trends in resection rates should be interpreted cautiously, because patient selection for surgery might reflect changes in diagnostics, overall treatment strategy or changes in the classification of tumours.

When pT and ypT categories were combined, no significant change in tumour category was seen over time. It is more likely that, as a result of neoadjuvant therapy, a greater proportion of initially more advanced tumours was treated surgically in recent years. Another explanation for the increasing number of oesophageal resections might have been classification of some gastro-oesophageal junctional tumours as oesophageal rather than gastric cancers. At most this can have had only a small effect as the increase in oesophageal resection rates was only partly offset by a decrease in gastrectomies, the latter largely being thought to reflect a decreasing gastric cancer incidence and improved preoperative staging [3]. The increase in number of resections in the Netherlands has mainly taken place in university and non-university teaching hospitals, a phenomenon that has been described before [13]. Since 2008, a yearly minimum of ten oesophagectomies per year, and in 2011 a minimum of 20 per hospital, was enforced by the Dutch Health Care Inspectorate. It has been shown that centralization improves patient selection, perioperative care, surgical experience and decreases 'failure to rescue'[19]. Although type of hospital was clearly associated with survival here, multivariable analysis showed that it did not contribute significantly to the observed trend of improved survival with time.

A shift towards more transthoracic resections was evident, but not associated with survival. This is in line with the findings of a randomized clinical trial [6] and a meta-analysis [20] comparing transhiatal and transthoracic oesophagectomy. The initial hypothesis that better nodal clearance might be associated with survival was confirmed in the present data. There was a significant improvement in nodal clearance from period 1 to period 3, although survival improvement was only seen between periods 1 and 2. The finding that survival did not change during period 2 and period 3 is noteworthy because many treatment and tumour-related variables changed at about this time (such as number of removed lymph nodes, tumour type and operation type). The number of nodes might be one of the factors contributing to the improved survival between periods 1 and 2, along with the introduction of the first centralization projects. The exact association between number of nodes and survival in the era of multimodal therapy is unclear as regressional changes are seen in lymph nodes after preoperative CRT.

The present study has several limitations. The analysis was limited by the clinicopathological data available. Missing data, especially for many patients in the earlier cohorts, meant that only a proportion of patients was left for studying the effects of variables. In the final model, the variable 'time period' was still a significant predictor of survival after adjusting for all the known variables. It has to be acknowledged, however, that stage, grade and involvement of surgical resection margins were not included in this model because of co-linearity of these variables with neoadjuvant therapy. Despite a limited study period of 12 years, small changes in case mix may have occurred over time, but this could not be examined as information on co-morbidity and performance status was not available.

Patient selection may also have biased these results. One possible explanation for the observed increase in survival is that patients undergoing resection in the latter periods represent a group with an earlier clinical stage, as demonstrated previously [21]. Improved

staging allowing the exclusion of occult metastatic disease by sophisticated diagnostics, and enhanced multidisciplinary treatment algorithms have previously been associated with survival [22,23], and may have had some effect, but the rising number of oesophagectomies over time would seem to contradict more careful patient selection. Although resectability rates for patients with newly diagnosed oesophageal cancer are not reported by the available registry, this trend might indicate a more aggressive surgical practice possibly instigated by the recent national volume standards in the Netherlands. In the present study, a potential shift in pathological staging across the different periods was impossible to analyse accurately because of the gradual increase in the use of neoadjuvant therapy. The present study only documented long-term survival. Because of privacy regulations only date of diagnosis was available. Therefore, short-term mortality related to surgery and/or neoadjuvant therapy could not be studied. Six-month mortality (as counted from date of diagnosis) for periods 1 to 4 was 12.8, 9.3, 7.5 and 6.1 per cent respectively, perhaps implying lower treatment-related mortality over time, although there is confounding here as a result of the increase in time between diagnosis and completion of surgical treatment. Other studies indicated that the postoperative 30-day mortality rate was 5.2 per cent around 2000 [24] and 4 per cent in 2010 [9]. Changes in postoperative mortality are not likely to explain the improved survival during the present study, as survival curves only diverged with longer follow-up (Fig. 1). Finally, owing to the chosen dates for the cohorts, 5-year survival cannot be reported for the most recent period (2008–2010).

Survival after oesophagectomy for cancer improved substantially between 1999 and 2010 in the Netherlands. Reasons for this improvement are probably multifactorial but, of all the studied prognostic variables that changed during the study interval, the introduction of neoadjuvant therapy was the most important.

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Table 1
Patient and tumour characteristics

	1999–2001 (*n* = 793)	2002–2004 (*n* = 1033)	2005–2007 (*n* = 1183)	2008–2010 (*n* = 1373)
Age (years)*	60 (54–68)	60 (55–67)	60 (54–68)	62 (56–68)
Sex ratio (M : F)	587 : 206	797 : 236	12 : 271	1065 : 308
Hospital type				
University	331 (52.5)	433 (47.3)	540 (46.6)	596 (44.3)
Non-university, teaching	250 (39.6)	432 (47.2)	572 (49.3)	714 (53.0)
Non-teaching	50 (7.9)	51 (5.6)	48 (4.1)	36 (2.7)
Missing	162	117	23	27
Tumour location				
Middle third	148 (18.7)	154 (14.9)	164 (13.9)	174 (12.7)
Lower third/OGJ	623 (78.6)	843 (81.6)	977 (82.6)	1142 (83.2)
Not specified	22 (2.8)	36 (3.5)	42 (3.6)	57 (4.2)
Tumour type				
Squamous cell carcinoma	267 (33.7)	311 (30.1)	318 (26.9)	317 (23.1)
Adenocarcinoma	526 (66.3)	722 (69.9)	865 (73.1)	1056 (76.9)
Tumour differentiation				
Good	47 (5.9)	46 (4.5)	49 (4.1)	43 (3.1)
Moderate	309 (39.0)	391 (37.9)	407 (34.4)	336 (24.5)
Poor	357 (45.0)	442 (42.8)	538 (45.5)	515 (37.5)
Not specified	80 (10.1)	154 (14.9)	189 (16.0)	479 (34.9)
Neoadjuvant therapy				
None	615 (77.6)	771 (74.6)	917 (77.5)	591 (43.0)
Chemotherapy only	150 (18.9)	158 (15.3)	140 (11.8)	241 (17.6)
Chemoradiotherapy	28 (3.5)	104 (10.1)	126 (10.7)	541 (39.4)
Operation type				
Transhiatal resection	121 (62.7)	265 (67.1)	588 (54.2)	674 (52.0)
Transthoracic resection	72 (37.3)	130 (32.9)	496 (45.8)	622 (48.0)
Missing	600	638	99	77

pT category				
pT1	126 (15.9)	148 (14.3)	160 (13.5)	139 (10.1)
pT2	139 (17.5)	142 (13.7)	155 (13.1)	105 (7.6)
pT3	312 (39.3)	446 (43.2)	566 (47.8)	332 (24.2)
pT4	17 (2.1)	18 (1.7)	30 (2.5)	8 (0.6)
Not specified	21 (2.6)	17 (1.6)	6 (0.5)	7 (0.5)
ypT category				
ypT0	15 (1.9)	22 (2.1)	51 (4.3)	171 (12.5)
ypT1	28 (3.5)	32 (3.1)	23 (1.9)	111 (8.1)
ypT2	29 (3.7)	59 (5.7)	54 (4.6)	145 (10.6)
ypT3	76 (9.6)	119 (11.5)	113 (9.6)	282 (20.5)
ypT4	5 (0.6)	4 (0.4)	1 (0.1)	10 (0.7)
Not specified	25 (3.2)	26 (2.5)	24 (2.0)	63 (4.6)
Involvement of surgical resection margins†	365 (84.1)	553 (83.4)	936 (84.3)	1170 (90.0)
R0	69 (15.9)	110 (16.6)	174 (15.7)	130 (10.0)
R1/R2	359	370	73	73
Missing	8 (4–13)	9 (5–15)	13 (9–18)	15 (10–20)
No. of removed lymph nodes*				
≤ 7	293 (36.9)	343 (33.2)	220 (18.6)	217 (15.8)
8–12	193 (24.3)	248 (24.0)	289 (24.4)	330 (24.0)
13–18	119 (15.0)	185 (17.9)	305 (25.8)	350 (25.5)
≥ 19	56 (7.1)	145 (14.0)	311 (26.3)	438 (31.9)
Not specified	132 (16.6)	112 (10.8)	58 (4.9)	38 (2.8)
No. of lymph involved nodes				
None (N0)	324 (40.9)	440 (42.6)	502 (42.4)	737 (53.7)
1–2 (N1)	186 (23.5)	261 (25.3)	267 (22.6)	292 (21.3)
3–6 (N2)	129 (16.3)	183 (17.7)	232 (19.6)	198 (14.4)
> 6 (N3)	73 (9.2)	85 (8.2)	157 (13.3)	123 (9.0)
Not specified	81 (10.2)	64 (6.2)	25 (2.1)	23 (1.7)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). † R1/R2, microscopic or macroscopic involvement of resection margins. OGJ, oesophagogastric junction.

Table 2
Two- and 5-year overall survival rates for patients who underwent oesophagectomy for cancer between 1999 and 2010

		No. of patients	2-year survival (%)	5-year survival (%)	*P* for 5-year survival*
Time period of surgery	1999–2001	793	49.3	28.0	< 0.001
	2002–2004	1033	58.4	33.6	
	2005–2007	1183	56.2	33.2	
	2008–2010	1373	61.0	n.a.	
Age (years)	< 55	855	61.0	39.8	< 0.001
	55–64	1558	60.6	34.2	
	65–74	1467	54.1	29.6	
	≥ 75	502	45.4	23.5	
Sex	F	1021	61.4	37.5	< 0.001
	M	3361	55.4	31.2	
Hospital type	University	1900	61.4	38.5	< 0.001
	Non-university, teaching	1968	55.8	30.2	
	Non-teaching	185	45.2	23.4	
	Missing	329	51.7	27.9	
Tumour location	Middle third	640	57.0	32.1	0.273
	Lower third/OGJ	3585	57.0	33.7	
	Not specified	157	49.3	29.2	
Tumour type	Squamous cell carcinoma	1213	56.1	34.0	0.554
	Adenocarcinoma	3169	58.6	34.4	
Tumour differentiation	Good	185	75.1	59.2	< 0.001
	Moderate	1443	61.0	35.4	
	Poor	1852	46.5	24.2	
	Not specified	902	69.6	46.0	
Neoadjuvant therapy	None	2894	52.8	30.9	< 0.001
	Chemotherapy only	689	63.6	38.4	

	Chemoradiotherapy	799	68.6	44.9	
Operation type	Transhiatal resection	1648	58.8	36.4	0.692
	Transthoracic resection	1320	59.5	34.8	
	Missing	1414	54.0	30.3	
pT category	pT1	573	79.6	63.3	< 0.001†
	pT2	541	59.3	31.2	
	pT3	1656	43.0	19.0	
	pT4	73	15	7	
	Not specified	51	55	30	
ypT category	ypT0	259	80.8	61.0	
	ypT1	194	75.2	54.5	
	ypT2	287	70.1	44.3	
	ypT3	590	53.2	25.1	
	ypT4	20	9	0	
	Not specified	138	72.7	58.3	
Involvement of surgical resection margins	R0	3024	63.7	38.0	< 0.001
	R1/R2	483	33.6	13.5	
	Missing	875	50.0	27.6	
No. of removed lymph nodes	≤ 7	1073	55.2	32.3	< 0.001
	8–12	1060	55.1	31.0	
	13–18	959	57.7	33.8	
	≥ 19	950	60.0	39.8	
	Not specified	340	55.8	30.3	
No. of involved lymph nodes	None (N0)	2003	75.1	53.3	< 0.001
	1–2 (N1)	1006	50.6	23.0	
	3–6 (N2)	742	39.2	12.5	< 0.001
	> 6 (N3)	438	23.1	5.4	
	Not specified	193	57.2	30.3	

n.a., Not applicable; OGJ, oesophagogastric junction. *Logrank; †pT/ypT combined

Table 3
Multivariable Cox models evaluating time trends in survival of patients who underwent oesophagectomy for cancer between 1999 and 2010

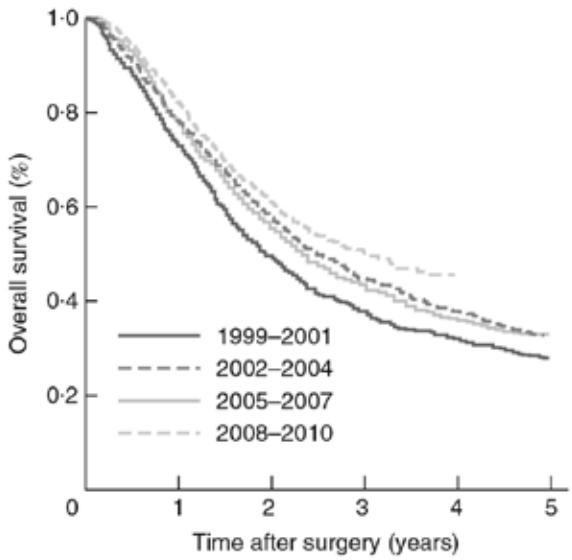
	Variable	Hazard ratio				x^2 for time period in the model
		1999–2001	2002–2004	2005–2007	2008–2010	
Model 1	Unadjusted	1.00 (reference)	0.85 (0.77, 0.95)	0.86 (0.78, 0.96)	0.71 (0.64, 0.80)	34
Model 2	Adjusted for hospital type	1.00 (reference)	0.86 (0.77, 0.95)	0.88 (0.79, 0.98)	0.72 (0.64, 0.81)	30
Model 3	Adjusted for tumour differentiation	1.00 (reference)	0.85 (0.76, 0.94)	0.85 (0.76, 0.94)	0.74 (0.66, 0.84)	25
Model 4	Adjusted for neoadjuvant therapy	1.00 (reference)	0.86 (0.78, 0.96)	0.86 (0.78, 0.96)	0.80 (0.71, 0.90)	15
Model 5	Adjusted for (y)pT category	1.00 (reference)	0.82 (0.73, 0.91)	0.79 (0.71, 0.88)	0.79 (0.70, 0.88)	23
Model 6	Adjusted for involvement of surgical resection margins	1.00 (reference)	0.84 (0.76, 0.94)	0.89 (0.79, 0.99)	0.78 (0.69, 0.88)	18
Model 7	Adjusted for no. of nodes removed	1.00 (reference)	0.86 (0.77, 0.96)	0.89 (0.80, 0.99)	0.74 (0.66, 0.84)	25
Model 8	Adjusted for no. of nodes involved	1.00 (reference)	0.84 (0.76, 0.94)	0.78 (0.70, 0.87)	0.75 (0.66, 0.84)	28
Model 9	Full model*	1.00 (reference)	0.86 (0.77, 0.96)	0.86 (0.76, 0.95)	0.91 (0.74, 1.02)	8

Values in parentheses are 95 per cent c.i. *Full model included: age, sex, time period of surgery, hospital type, neoadjuvant therapy, number of removed nodes and number of involved nodes.

Supplementary Table 1
Six-month overall mortality rates of 4 382 patients who underwent oesophagectomy for cancer between 1999 and 2010 in the Netherlands.

Time period of surgery	N	6-month mortality rate (%)
1999-2001	793	12
2002-2004	1033	9
2005-2007	1183	7.5
2008-2010	1373	6.1

Figure 1
Kaplan–Meier overall survival curves for patients who underwent oesophagectomy for cancer according to time interval: 1999–2001 (period 1), 2002–2004 (period 2), 2005–2007 (period 3) and 2008–2010 (period 4). P <0·001 (overall, 2005–2007 versus 2008–2010, and 1999–2001 versus 2002–2004) (log rank test)



No. at risk

1999–2001	793	579	391	299	253	221
2002–2004	1033	804	594	460	389	335
2005–2007	1183	915	657	509	423	243
2008–2010	1373	1123	563	212	0	

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Chapter 8

Future perspectives

FUTURE PERSPECTIVES

The rising incidence of adenocarcinoma in the West is impressive. If the yearly increase stays at the current level, the incidence of oesophageal cancer will potentially surpass that of colon cancer in the future. Much improvement has been achieved by oesophageal cancer research during the last decades. However, there are many remaining battles to win and some of these will be discussed in this chapter.

Future perspectives on surgery

Although, also in the near future, surgical treatment will be the mainstay of treatment for potentially curable disease, there will be further important advances in nonsurgical therapies. The direction will be towards organ-sparing options in situations where that is oncologically safe and appropriate.

Definitive chemoradiotherapy (dCRT) is expected to be increasingly performed, even in patients with resectable oesophageal cancer. Resection will then be only considered for incomplete responders or patients with local or regional recurrence. The trials by Stahl and Bedenne which compared dCRT versus neoadjuvant chemoradiotherapy (nCRT) plus surgery have already led to a paradigm shift in the management of squamous cell carcinoma in some countries [1,2]. In the future, this algorithm may also be applicable to patients with adenocarcinoma because of better nonsurgcial treatment regimens.

In the future, waiting a longer period after neoadjuvant therapy will be more frequently applied, thereby offering the possibility of patient recovery, increasing the chance of properly assessing a complete clinical response and, hence, a better patient selection for surgery.

Surgery might be increasingly regarded as ‘adjuvant’ to the other treatment strategies. Local recurrence is still not uncommon after dCRT, thus suggesting the potential need of ‘salvage’ surgery in patients receiving this treatment. Previous studies have reported salvage oesophagectomies to result in long-term survival in a subset of patients [3]. However, the data are ambiguous regarding the mortality, morbidity, and length of hospital stay after these procedures. Future research should be devoted to salvage oesophagectomies in order to obtain more evidence on surgical and oncological safety.

Without doubt, minimally invasive surgery will further evolve, which has been proven to be superior to open surgery regarding postoperative pulmonary complication rate, short-term quality of life [4] with comparable short-term oncological outcome parameters. Besides the need for studies reporting long-term outcomes of minimally invasive surgery, there are some other important questions to answer in the future. The future surgical debate will focus on the best technique, which will probably be a composition of different ingredients: minimally invasive versus transhiatal versus open oesophagectomy, regional lymph node sampling versus en bloc radical lymphadenectomy, and intrathoracic versus cervical oesophagogastric anastomoses. Evolving technology might allow image-guided surgery and also identification

of involved nodal groups.

Based on this thesis, an extended lymphadenectomy after neoadjuvant chemoradiotherapy (nCRT) is debatable, but further adequately powered large RCTs are needed to determine the appropriate extent of a lymphadenectomy during potentially curative oesophagectomy after neoadjuvant treatment. It is an interesting discussion what the exact role is of minimally invasive surgery if a transhiatal approach with a limited mediastinal lymph node harvest is really sufficient after nCRT. However, when an intrathoracic oesophagogastric anastomosis is preferred over a cervical anastomosis, a thoracoscopy/-tomy will still be indespensible.

Future perspectives on staging

Despite currently available techniques to stage oesophageal cancer (e.g. EUS, PET/CT), there is still a need for better patient selection. Especially better re-staging techniques after or during neoadjuvant therapy are needed in the future. With the implementation of neoadjuvant treatment, the traditional prognostic factors including tumour stage and grade have become less powerful as they change because of the therapy. It is increasingly evident that residual cancer present in the resected surgical specimen (especially in the removed lymph nodes) after preoperative therapy (particularly CRT) is the main determinant of the patient's long-term outcome. The key issue of prognosis will therefore be response prediction. With future metabolic and target-specific imaging, tumour biology will be monitored during treatment and patients will be categorized in a clinically more relevant manner than nowadays, i.e. based on the therapy that is likely to be effective, thus avoiding ineffective, toxic and expensive treatments.

The conventional diagnostic modalities have their limitations in response prediction. EUS is limited by no-pass (due to tumour stenosis) in some patients and EUS-FNA is difficult to distinguish tumour from fibrosis. CT imaging has difficulties in distinguishing between viable tumour and treatment induced inflammatory tissue and fibrosis. However, the technical developments in serial PET scanning are particularly interesting because they also provide characteristics of the clinical biology of oesophageal cancer undergoing therapy. More research is needed before restaging with PET allows for treatment decisions e.g. on an organ-preserving strategy versus discontinuation of neoadjuvant therapy and proceeding to surgery. Several studies have already demonstrated that PET/CT may be more accurate than EUS-FNA and CT alone in the evaluation of therapeutic response to neoadjuvant CRT and the detection of residual tumour deposits [5, 6, 7]. Therefore, in the future, PET/CT will gain influence in initial staging because adequate comparison with a pretreatment PET/CT will be important for proper assessment of therapeutic response after CRT.

There are also new developments in the imaging quality of MRI suggesting a more important role in staging and restaging in the future. Recent pilot studies showed that functional MRI techniques might compensate for the limitations inherent to other imaging devices [8].

Biological parameters will be also involved in the future of response prediction, adding power to conventional predictive modalities. Although some biomarkers are associated with pathologic response, currently these are not yet well established, especially because their specificity is too low for clinical implementation [9]. In the future, the combination of biomarkers and tumour genetic profiles will reveal a better prediction of oncological outcome. Microarrays for gene expression will disclose important prognostic information.

Until now, there is insufficient evidence to allow for individualized selective lymphadenectomy and sentinel lymph node navigation in oesophageal surgery. Although sentinel node navigation surgery is feasible, its application in the gastrointestinal tract is still controversial [10]. However, innovation including the development of new tracers can be expected which may improve the accuracy and reliability of SLN mapping in oesophageal cancer in the future. Since the magnitude of the operative insult experienced during a systematic lymphadenectomy is considerable, the introduction of sentinel node navigation surgery could thus reduce the mortality and morbidity in patients undergoing an oesophagectomy and preserve the patients' quality of life.

Currently, the 8th edition of the Union for International Cancer Control – American Joint Committee on Cancer (UICC-AJCC) tumour, node, metastases (TNM) staging system is developed to provide an even more accurate staging system. The current 7th edition is based on data from patients treated with surgery alone. Response to neoadjuvant therapy should clearly be incorporated in the next edition. Based on the results of this thesis, re-introduction of the location of nodal involvement in the staging system might be considered.

Future perspectives on survival

Prevention of oesophageal cancer is of paramount importance. Better understanding on the specific causes underlying the development of especially adenocarcinoma will fuel preventive strategies. In the first place, there is a great need to stop the obesity epidemic, which has been strongly related to developing oesophageal cancer [11].

Oesophageal cancer is commonly diagnosed at an advanced stage, resulting in poor prognosis. Early detection offers possibilities to intervene in the disease progression at an earlier stage. More research should be devoted to improve surveillance of patients with Barrett's metaplasia including individual risk stratification. Molecular studies are promising and various genetic polymorphisms have already been identified [12].

Future improvements in long-term survival in oesophageal cancer can be expected from more sophisticated neoadjuvant and adjuvant treatment regimens. The results of the CROSS trial are consistent with a model in which systemic therapy reduces the risk of distant metastases, and combined CRT improves locoregional control, further increasing cure rate by reducing the risk of recurrence in patients without systemic disease, and by

eliminating residual primary tumour cells as a source of potential subsequent dissemination [13]. The approach taken in the CROSS trial emphasizes the importance of controlling both systemic and locoregional disease. Further improvements are still desperately needed and may result from identifying molecular subtypes that are sensitive to targeted agents such as antibody and small molecule kinase inhibitors or immune modulators. Exploring individualized multimodal treatment is clearly the most promising strategy for further improving outcome of oesophageal cancer therapy.

Future research projects should also be devoted to the differences between squamous cell carcinoma (SCC) and adenocarcinoma (AC). Long-term survival rates between the two subtypes differ because of different responses to neoadjuvant therapy. For example, definitive chemoradiotherapy is considered as an alternative to surgery for SCC but not for AC. The future of neoadjuvant therapy may therefore include different treatment strategies for the two histological subtypes, which requires further investigation.

Further improvement can be expected from the spin-off of the molecular revolution. An increasing number of studies try to identify the pathways that are up- or downregulated in oesophageal cancer or during neoadjuvant therapy in order to manipulate these pathways in the future [14].

In future research projects, quality of life (QoL) should become a more important endpoint. The functional outcome after oesophagectomy has only recently begun to attract appropriate attention. The functional disturbances after oesophagectomy are measured in terms of dysphagia, regurgitation, early satiety, and dumping symptoms which may be profound. Improved tools for the assessment of quality of life and functional outcome are needed to define a “success” after oesophagectomy or chemoradiotherapy (CRT) [15, 16]. It is too simple to conclude that by definition organ-preserving treatment strategies inherently offer a better quality of life when compared to surgical modalities. A recent study showed that oesophagectomy and definitive CRT provided comparable functional results at 24 months of follow-up, except for progressive decline in pulmonary function in the CRT group, likely the result of radiation pneumonitis [17].

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Chapter 9

Summary | Samenvatting

ENGLISH SUMMARY

This thesis includes studies that investigate different aspects of oesophageal cancer: surgical treatment, staging and survival after surgery. It is subdivided in three parts: Goals of surgical therapy for oesophageal cancer (Part I), Aspects of staging of oesophageal cancer based on lymph node involvement (Part II) and Aspects of survival in oesophageal surgery (Part III).

PART I: GOALS OF SURGICAL THERAPY FOR OESOPHAGEAL CANCER

The treatment of patients with oesophageal cancer is complex and demands a multidisciplinary approach, in which potential treatment strategies are tailored to the individual patient. Surgery is still the cornerstone of potentially curative treatment. Nevertheless, less than half of the patients actually can be offered surgical treatment. In the remaining patients surgery is futile at first presentation because of concurrent distant metastases.

Oesophagectomy is probably one of the most challenging procedures in surgery. **Chapter 2** covers the main goals that have been defined for 'open' oesophagectomy and are also applicable to the increasingly used minimally invasive oesophagectomy. The following issues are highlighted: resection margin involvement, pros and cons of limited versus extended lymphadenectomy, restoration of gastrointestinal continuity, morbidity and mortality. The importance of auditing surgical quality is underlined.

Special attention is paid to the role of lymphadenectomy as an introduction to the following chapters of the thesis. Although a transthoracic surgical approach is associated with an increased number of lymph nodes in the surgico-pathological specimen - which has previously been related to better survival in literature - a benefit of a transthoracic approach over a transhiatal approach has not unequivocally been shown in trials and reviews.

Finally, in chapter 2 a paragraph has been devoted to definitive chemoradiotherapy as an alternative for potentially curative resection.

PART II: ASPECTS OF STAGING OF OESOPHAGEAL CANCER BASED ON LYMPH NODE INVOLVEMENT

Oesophageal cancer is an aggressive disease with a dismal prognosis. Five-year survival for the whole population with newly diagnosed oesophageal cancer is around 10%. The poor prognosis is related to the advanced stage of disease at presentation. Accurate staging of tumour extension is essential, not only locally (through the wall of the oesophagus) but also regionally (in the lymph nodes surrounding the oesophagus) and distantly (spread to other organs). Traditionally, staging of malignant tumours is based on the Tumour, Nodes, Metastases (TNM-) classification.

Preoperative clinical staging, which frequently encompasses a combination of investigations including endoscopy, endoscopic ultrasonography and (PET-)CT scanning, can detect that there are distant metastases making surgery futile. On the other hand clinical staging can also show that the disease is at a very early stage, which can potentially be cured by an endoscopic organ-preserving resection.

In **chapter 3** two research questions are addressed. In the first place, it was investigated whether clinical staging could actually predict patients' prognosis. A study population of 102 patients from Rotterdam and Cambridge was clinically staged by endoscopic ultrasonography (EUS). It was shown that EUS could identify lymph node metastases as well as their location (esp. whether the involved lymph nodes were located above, below or on both sides of the diaphragm). Moreover, it was pointed out that involved metastases identified on both sides of the diaphragm were associated with a relatively poor prognosis compared to patients in whom EUS had not identified involved lymph nodes or only at one side of the diaphragm. These results showed that preoperative EUS is valuable in the decision to embark upon a surgical resection or to choose for a palliative treatment instead.

Secondly, it was evaluated whether this prognostic impact of distribution of involved nodes relative to the diaphragm also exists when determined in the resected specimen as assessed by the pathologist (pathological staging). Some 327 patients who had undergone oesophagectomy for cancer were included, their pathology reports reviewed (including the location of lymph node involvement) and subsequently related to long-term survival. With this analysis it was shown that a combined staging system that incorporates both number and distribution of lymph nodes relative to the diaphragm refines prognostication after oesophagectomy. This conclusion has the opportunity to counsel patients about their prognosis more precisely.

In the previous 6th edition of the TNM staging system (TNM6) no distinction was made between distant organ metastases and 'non-regional' lymph node metastases (e.g. celiac node involvement), which were both categorized as being M1. The exact definition of regional and non-regional was unclear and this principle has been abandoned in the most recent 7th edition of the TNM staging system (TNM7). Furthermore TNM7 has acknowledged the importance of the number of involved nodes by subdividing the N-classification into N0 to N3. The new staging system was built on data from thousands of oesophageal cancer patients in whom squamous cell carcinoma was predominant and surgical approach was most frequently transthoracic. In **Chapter 4** the validation of TNM 7 is described in a Rotterdam cohort of 358 adenocarcinomas who underwent a transhiatal approach. This study indicated that the application of the 7th TNM staging system results in a better prognostic stratification of overall survival compared to the 6th edition. The fact that TNM7 also had a superior prognostic ability in this study population from a single high-volume institution with predominantly adenocarcinomas and a transhiatal approach supports its generalizability for different oesophageal cancer practices. Although patients underwent a transhiatal oesophagectomy with a modest lymph node harvest (median 11), the survival curves of the

different N-stages did not overlap in these data, which probably indicated that the lymph node sampling was valid and robust. Finally, it was concluded that patients with 'non-regional' lymph node metastases had a dismal prognosis, but still significantly better than patients with distant metastases.

During recent years it has been generally accepted that, in case of locally advanced disease, surgery alone is not able to cure the patient but should be accompanied by other modalities such as chemotherapy and radiotherapy. The Dutch randomised controlled CROSS trial showed that a multimodality treatment including surgery after neoadjuvant chemoradiotherapy increases long-term survival. A considerable percentage of patients even showed a pathologically complete response and a beneficial impact on lymph node metastases was also shown: more than half of the patients with involved lymph nodes in the surgery-alone arm could be nodally 'sterilised' by chemoradiotherapy. In **Chapter 5** a study is described that was based upon the CROSS trial database. In this study, the positive impact of an extended lymphadenectomy on survival, as shown by other studies, could be reproduced for patients who underwent surgery alone. However, in the patients who underwent surgery after neoadjuvant chemoradiotherapy, the number of resected nodes was not associated with survival. These data question the indication for maximisation of lymoh node dissection after chemoradiotherapy for staging purposes as well as for therapeutic reasons. Whether a transhiatal approach suffices after chemoradiotherapy needs to be further investigated.

PART III: ASPECTS OF SURVIVAL IN OESOPHAGEAL SURGERY

Resection of the oesophagus is associated with a relative high morbidity and even mortality. There is an increasing interest in performance indicators as instruments for comparing quality of care between institutions. The performance indicator that was studied in **chapter 6** is postoperative mortality. The medical files of patients who underwent oesophagectomy between 1991 and 2011 were reviewed and the patients were identified who died within 1 year after surgery. Subsequently, the complication was chosen that contributed most to the patient's death. This study shows that a substantial number of deaths after the traditional cut-off of 30 days after surgery could still be related to complications related to the procedure such as anastomotic leakage and 'sudden death'. On the other hand, extending the follow-up beyond 90 days after surgery resulted mainly in the inclusion of more patients who died of recurrent disease as opposed to medical or technical complications related to surgery. Of course the early (surgery-related) as well as the late (oncological) outcomes are important when comparing quality of care. One of the conclusions was that it would be helpful if hospital performance in oesophageal surgery would include 90-day mortality along with 1-year survival, thus reflecting the quality of both the diagnostic and the therapeutic process.

Although long-term survival for oesophageal cancer has improved during the past decades, surgery still does not guarantee survival and 5-year survival rarely exceeds 40%.

In **Chapter 7** a study is described based on oesophageal cancer patients from the Dutch Cancer Registry between 1999 and 2010. A rise in the number of surgical resection, as has been shown in various cancer registries worldwide, was also reported in this study with an almost two-fold rise during the study period. Furthermore, the study confirmed a significant increase in long-term survival, especially between periods 1999-2001 and 2002-2004 and again between periods 2005-2007 and 2008-2010. The factors explaining these trends were investigated. Although a better survival was reported in academic and non-academic teaching hospitals as compared to non-teaching hospitals, centralisation of this type of surgery could not explain the improved prognosis. The increase in the number of transthoracic surgical approaches could neither account for it. The main conclusion was that the most recent improvement in survival could particularly be explained by the introduction of neoadjuvant chemoradiotherapy. Finally, the main conclusions of the randomised CROSS trial (i.e. the high proportion of patients with pathologically complete response and the rise in the microscopically radical resection rate) were corroborated in this national database on population-based level.

In **Chapter 8** the most important future perspectives are described in view of the previous chapters.

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Dit proefschrift omvat onderzoeken die verschillende aspecten van slokdarmkanker belichten: de chirurgische behandeling van de ziekte, de stadiëring en de overleving na een operatie. Het proefschrift bestaat uit drie delen: Deel 1 – Eindpunten van chirurgische behandeling van slokdarmkanker, Deel 2 - de stadiëring op basis van lymfekliermetastasen bij slokdarmkanker, en Deel 3 - overleving na een operatie voor slokdarmkanker.

DEEL 1 : EINDDOELEN VAN CHIRURGISCHE BEHANDELING VAN SLOKDARMKANKER

De behandeling van patiënten met slokdarmkanker is complex en vereist een multidisciplinaire aanpak, waarbij behandelingsstrategieën in toenemende mate zijn gericht op de individuele patiënt. Een operatieve ingreep blijft de belangrijkste pijler binnen de behandeling. Echter, van de patiënten bij wie de diagnose slokdarmkanker wordt gesteld, komt slechts minder dan de helft in aanmerking voor een behandeling waarbij genezing kan worden verwacht. Een resectie van de slokdarm is alleen zinvol indien deze in opzet curatief kan zijn en er geen sprake is van ‘metastasen op afstand’.

De slokdarmresectie wordt beschouwd als een van de meest uitdagende operaties voor de ervaren chirurg. In **Hoofdstuk 2** worden de belangrijkste einddoelen besproken zoals deze in de literatuur geformuleerd zijn voor de conventionele open slokdarmresectie, maar die feitelijk ook gelden voor de steeds frequenter toegepaste minimaal-invasieve slokdarmresectie. Aan de orde komt het wetenschappelijk bewijs voor achtereenvolgens : het belang van tumorvrije chirurgische snijvlakken, de keuze voor een beperkte of juist meer uitgebreide lymfeklierdissectie, continuïteitsherstel van het spijsverteringskanaal en het beperken van postoperatieve complicaties en sterfte.

De paragrafen over lymfeklierdissectie en chirurgische benadering zijn relatief uitgebreid in hoofdstuk 2 als inleiding op de hierna volgende hoofdstukken. Een gecombineerde thoracale en abdominale benadering van de slokdarm resulteert in het algemeen in het hoogste aantal lymfeklieren in het uiteindelijke operatie preparaat zoals beoordeeld door de patholoog, omdat hierbij ook de lymfeklierstations hoog in de thorax (=borstholte) kunnen worden verwijderd. In de literatuur is een hoger aantal verwijderde lymfeklieren in verband gebracht met een verbeterde overleving. Er is echter nooit een duidelijk voordeel onomstotelijk aangetoond van een gecombineerde ten opzichte van een uitsluitend abdominale benadering. In meerdere onderzoeken werd geen verschil in overleving op lange termijn gevonden.

Er is een aanzienlijke kans op complicaties en zelfs sterfte na een slokdarmresectie. Het belang van kwaliteitsregistraties wordt hierbij onderstreept. De relatief hoge morbiditeit en mortaliteit kunnen o.a. worden teruggevoerd op de anatomische ligging van de slokdarm naast de vitale structuren in de hals, de borstholte en buik (abdomen). Een operatie vanwege een slokdarmtumor wordt dan ook vaak uitgevoerd in minstens twee van deze gebieden,

afhankelijk van de lokalisatie van de tumor en de conditie van de patiënt. Soms kan de meer kwetsbare patiënt een ingrijpende toegang via de zijkant van de (rechter) borstholte worden bespaard door vanuit de buik het thoracaal gelegen deel van de slokdarm los te maken. Een thoracale benadering daarentegen biedt een beter zicht op de structuren, die 'scherp' van de slokdarm kunnen worden losgemaakt. Uiteraard dient na verwijdering van vrijwel de gehele slokdarm de continuïteit van het spijsverteringskanaal te worden hersteld. Vaak geschiedt dit met behulp van de zogenaamde 'buismaag' die met een naad wordt aangesloten op de resterende slokdarm hoog in de thorax of laag in de hals. O.a. vanwege de vaak gecompromitteerde bloedvoorziening in de top van de buismaag bestaat er ter plaatse van deze naad een risico op lekkage met grote negatieve gevolgen.

Tot slot is in hoofdstuk 2 een paragraaf gewijd aan definitieve chemoradiotherapie, die in sommige landen wordt beschouwd als een alternatief voor chirurgie maar in Nederland alleen wordt toegepast bij patiënten die te kwetsbaar zijn voor een operatie.

DEEL 2 : STADIËRING VAN LYMFEKLIER METASTASEN BIJ SLOKDARMKANKER

Slokdarmkanker is een agressieve ziekte met een slechte prognose. Voor de gehele populatie patiënten die zich presenteert met een slokdarmtumor is de 5-jaarsoverleving ongeveer 10%. De slechte prognose hangt samen met het gevorderde stadium waarin de tumor zich bevindt op het moment dat de patiënt zich presenteert met klachten van de tumor, met name een bemoeilijkte passage van voedsel. Reeds in een vroeg stadium van de ziekte kan slokdarmkanker aanleiding geven tot uitzaaiingen (zgn. 'metastasen') naar plaatsen elders in het lichaam, bijvoorbeeld lymfeklieren of lever. Nauwgezette stadiëring van tumoruitbreiding, zowel lokaal (in de wand van de slokdarm) als regionaal (in de lymfeklieren in de nabijheid van de slokdarm) en op afstand (naar andere organen) is essentieel, omdat het ziektestadium niet alleen de prognose maar ook de behandelingsstrategie sterk beinvloedt.

Onder "klinische stadiëring" wordt verstaan de serie onderzoeken (vaak een combinatie van endoscopie, endoscopische echografie en (PET-)CT onderzoek) die plaatsvindt vòòr de behandeling op basis waarvan wordt bepaald wat de juiste behandeling is voor de individuele patiënt. Stadiëring kan bijvoorbeeld uitwijzen dat er sprake is van metastasen in andere organen. In dat geval hebben patiënten geen baat bij een operatie. Resectie van de slokdarm wordt immers niet beschouwd als een adequate palliatieve behandeling. Anderzijds kan geconstateerd worden dat er sprake is van een zeer vroeg stadium van slokdarmcarcinoom, waardoor het potentieel curatief behandeld zou kunnen worden met endoscopische orgaan-sparende resectie. Traditioneel worden kwaadaardige tumoren gestadieerd volgens de zogenaamde TNM classificatie. Het T(umor)-stadium representeert de diepte ingroei van de tumor in de wand van de slokdarm, het N(ode)-stadium representeert het aantal betrokken lymfeklieren en het M(etastase)-stadium representeert de aan- of afwezigheid van metastasen op afstand. Het TNM stadium dat gebaseerd is op de preoperatieve stadiëring wordt aangegeven met het c(linical)TNM stadium.

In **Hoofdstuk 3** worden twee onderzoeksvragen behandeld. In de eerste plaats is onderzocht of klinische stadiëring daadwerkelijk in staat is de prognose van patiënten te voorspellen. Bij 102 patiënten uit Rotterdam en Cambridge werd onderzocht of er sprake was van lymfekliermetastasen middels een preoperatieve echografie vanuit het lumen van de slokdarm (endoscopische ultrasonografie; EUS), waarmee de wand van de slokdarm alsmede de lymfeklieren om de slokdarm heen kunnen worden beoordeeld. EUS bleek in staat te zijn om uitzaaiingen van het slokdarmcarcinoom aan te tonen in lymfeklieren aan beide zijden van het middenrif. Bovendien bleek dit van voorspellende waarde te zijn voor een relatief korte overleving ten opzichte van patiënten bij wie EUS had uitgewezen dat er geen lymfekliermetastasen waren of 'slechts' aan één zijde van het middenrif. Dit betekent dat de EUS resultaten meegewogen kunnen worden bij de beslissing af te zien van een operatie en te kiezen voor een palliatieve behandeling.

Ten tweede werd onderzocht of deze prognostische betekenis van de verdeling van lymfekliermetastasen ten opzichte van het middenrif ook geldt bij onderzoek van het weefselpreparaat dat uiteindelijk na de operatie is verkregen (bestaande uit slokdarm, het bovenste deel van de maag en de omgevende lymfeklieren). Het bepalen van de tumor uitbreiding op basis van macroscopie en microscopie door de patholoog wordt "histopathologische stadiëring" genoemd. Deze wordt geclassificeerd volgens het p(athological)TNM stadium. Uit de pathologie verslagen van 327 patiënten werden zowel de lokalisatie als het aantal aangedane lymfeklieren geïnventariseerd en gerelateerd aan de overleving op lange termijn. Op deze manier kon worden aangetoond dat de ligging van de aangedane lymfeklieren ten opzichte van het middenrif prognostische informatie toevoegt aan de informatie betreffende het aantal aangedane lymfeklieren. Dit biedt de mogelijkheid de patiënt meer betrouwbaar te informeren over zijn of haar prognose.

Het N-stadium wordt bepaald door lymfeklieruitzaaiingen die aanwezig kunnen zijn niet alleen in de buurt ('regionaal'), maar ook op afstand van de tumor ('niet-regionaal'). Voorheen werd ervan uitgegaan dat lymfeklieruitzaaiingen op ruimere afstand van de primaire tumor net zo'n slechte prognose hebben als orgaanmetastasen. In de 6e editie van de TNM classificatie (TNM 6) werd bijvoorbeeld geen onderscheid gemaakt tussen een levermetastase of een 'niet-regionale' lymfeklier metastase – beide werden gestageerd als M1. Waar de grens lag tussen regionale metastasen en afstandsmetastasen voor lymfeklieren was echter niet erg duidelijk. Dit principe van 'niet-regionale' lymfeklieren is in de 7e editie van de TNM classificatie (TNM 7) verlaten. Bovendien is het N-stadium niet langer dichotoom (N0/N1), maar gebaseerd op het aantal gevonden lymfekliermetastasen (N0, N1, N2, N3). Deze meest recente editie is gebaseerd op een mondiaal bestand van duizenden slokdarmkanker patiënten, voor een belangrijk deel met plaveiselcelcarcinomen die transthoracaal werden verwijderd. De vraag was of deze resultaten konden worden gegeneraliseerd naar de Nederlandse situatie. **Hoofdstuk 4** beschrijft de validatie van TNM 7 in een Rotterdams cohort van 358 adenocarcinomen die uitsluitend transhiataal werden geopereerd. Ook in dit cohort bleek dat de overleving op lange termijn nauwkeuriger werd voorspeld door TNM

7 dan door de vorige TNM 6, hetgeen de generaliseerbaarheid onderstreept van de nieuwe editie van de TNM classificatie voor verschillende praktijkvoeringen wereldwijd. Ondanks het feit dat alle patiënten een transhiatale benadering ondergingen, met een relatief lage lymfeklieropbrengst, overlapten de overlevingscurves van N0, N1, N2 en N3 elkaar niet, waaruit de robuuste lymfeklierstadiëring van deze benadering blijkt. Bovendien kon worden geconcludeerd dat patiënten met 'niet-regionale' lymfeklieren weliswaar een slechte prognose hebben, maar dat bij deze patiënten de overleving echter wel significant beter is dan bij patiënten met metastasen op afstand.

In het algemeen wordt aangenomen dat als er sprake is van voortgeschreden ziekte (waarbij de tumor al door alle wandlagen heen is gegroeid en/of er sprake is van uitgebreide lymfekliermetastasering) chirurgie alleen vaak een onvoldoende behandeling is en gecombineerd dient te worden met andere modaliteiten zoals chemotherapie en radiotherapie. De histopathologische uitbreiding van de tumor die wordt vastgesteld in het operatiepreparaat na een dergelijke voorbehandeling wordt aangeduid met het ypTNM stadium. Het Nederlandse gerandomiseerde CROSS onderzoek heeft aangetoond dat, om de kans op overleving zo groot mogelijk te maken, een operatie dient voorafgegaan te worden door chemoradiatie. Niet alleen was er sprake van een complete tumor-respons bij een aanzienlijk percentage patiënten, ook bleek uit dit onderzoek het gunstige effect op lymfekliermetastasen: ten opzichte van de patiënten in de chirurgie-alleen arm werd bij de patiënten die eerst chemoradiatie ondergingen vaker 'sterilisatie' bereikt van de aangedane lymfeklieren. In **Hoofdstuk 5** wordt een onderzoek beschreven binnen de studiepopulatie van het CROSS onderzoek. Het positieve effect van uitgebreide lymfeklierdissecties, zoals dat in de literatuur is beschreven kon inderdaad worden gereproduceerd bij patiënten die alleen een operatie ondergingen. Maar er was geen relatie tussen het aantal verwijderde lymfeklieren en de overleving bij de 159 patiënten die een gecombineerde behandeling ondergingen van chemoradiatie plus een operatie. De noodzaak van uitgebreide lymfeklierdissecties nà chemoradiatie is derhalve twijfelachtig geworden. Of dit ook betekent dat een transhiatale benadering na chemoradiatie volstaat dient verder te worden onderzocht.

DEEL 3 : OVERLEVING NA EEN OPERATIE VOOR SLOKDARMKANKER

Een slokdarm resectie heeft een aanzienlijk risisco op postoperatieve morbiditeit en zelfs mortaliteit. Om dergelijke zorguitkomsten tussen ziekenhuizen te kunnen vergelijken is er een toenemende interesse in zgn. prestatie indicatoren. De prestatie indicator die wordt beschreven in **hoofdstuk 6** is postoperatieve sterfte. Van 1282 patiënten die tussen 1991 en 2011 werden geopereerd werden naast de overlijdensdatum ook de specifieke doodsoorzaken gescoord. Een aanzienlijk deel van de overleden patiënten overleden na het traditionele afkappunt van 30 dagen na de operatie, terwijl de doodsoorzaak desondanks nog wel moest worden toegeschreven aan een complicatie van de operatie, zoals een naadlekkage

of aan 'sudden death'. Voor de definitie van postoperatieve sterfte bleek het meer valide te zijn om een tijdsperiode te gebruiken van 90 dagen in plaats van 30 dagen na de operatie. Overigens waren er geen verschillen tussen de voorspellende factoren van 30-dagen en 90-dagen mortaliteit. Na het verstrijken van de 90-dagen periode werd het grootste aandeel van de sterfte verklaard door oncologische oorzaken, d.w.z. terugkeer van de ziekte. Uiteraard zijn zowel de vroege (operatie-gerelateerde) als de late (oncologische) uitkomsten beide van belang voor de vergelijking van de kwaliteit van zorg tussen ziekenhuizen. Het lijkt dan ook aangewezen bij kwaliteitsregistraties een combinatie van 90-dagen en 1-jaars mortaliteit in ogenschouw te nemen.

Hoewel de langetermijnoverleving voor slokdarmkanker door de jaren is toegenomen, biedt een operatie nog altijd geen garantie op genezing. De 5-jaars overleving na een in opzet curatieve slokdarmresectie is zelden hoger dan 40%. In **Hoofdstuk 7** wordt een onderzoek van slokdarmkanker patiënten beschreven uit de Nederlandse Kanker Registratie tussen 1999 en 2010. Een toename in de incidentie (het aantal nieuwe gevallen per jaar) van het slokdarmcarcinoom, zoals deze door kankerregistraties over de gehele wereld wordt gerapporteerd, werd ook in dit databestand gezien met een verdubbeling van het aantal slokdarmresecties gedurende de onderzoeksperiode. Er bleek sprake van een verbetering in de overleving, met name tussen de periodes 1999-2001 en 2002-2004 en opnieuw tussen de periodes 2005-2007 en 2008-2010. De verklarende factoren voor deze verbeteringen werden geanalyseerd. Hoewel in academische- en niet-academische opleidingsziekenhuizen een betere overleving werd gezien in vergelijking met niet-opleidingsziekenhuizen, kon de centralisatie van zorg de verbeterde overleving niet verklaren. Ook de toename in het aantal transthoracale chirurgische benaderingen was een onvoldoende verklaring. De meest recente verbetering in prognose werd vooral verklaard door de introductie van neoadjuvante chemoradiatie. De belangrijkste resultaten van het gerandomiseerde CROSS onderzoek, waaronder het percentage patiënten met een complete pathologische respons en met een radicale resectie, konden in dit landelijke onderzoek op populatie niveau worden gereproduceerd.

In **Hoofdstuk 8** worden de belangrijkste toekomstperspectieven geschetst in het licht van de beschreven onderzoeken.

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List of contributing authors

Dr. MI van Berge Henegouwen
Department of Surgery
Academic Medical Centre Amsterdam

Dr NR Carroll
Department of Radiology
Cambridge University Hospitals

CROSS Study Group

Dr. RAM Damhuis
Dutch Cancer Registry

Prof . Dr. RC Fitzgerald
MRC Cancer Unit
University of Cambridge

Dr. BA Grotenhuis
Department of Surgery
Erasmus MC Medical Centre Rotterdam

Drs. P van Hagen
Department of Surgery
Erasmus MC Medical Centre Rotterdam

Dr RH Hardwick
Department of Surgery
Cambridge University Hospitals

Prof. Dr. JJB van Lanschot
Department of Surgery
Erasmus MC Medical Centre Rotterdam

Dr. CWN Looman
Department of Public Health
Erasmus MC Medical Centre Rotterdam

Dr. HF Lingsma
Department of Public Health
Erasmus MC Medical Centre Rotterdam

Dr. X Liu
MRC Cancer Unit
University of Cambridge

Dr. CAJ Ong
MRC Cancer Unit
University of Cambridge

Dr. C Rosman
Department of Surgery
Canisius Medical Centre Nijmegen

Dr. MCW Spaander
Department of Gastroenterology
Erasmus MC Medical Centre Rotterdam

Prof. Dr. EW Steyerberg
Department of Public Health
Erasmus MC Medical Centre Rotterdam

Drs. J Shapiro
Department of Surgery
Erasmus MC Medical Centre Rotterdam

Prof. Dr. HW Tilanus
Department of Surgery
Erasmus MC Medical Centre Rotterdam

Dr. BPL Wijnhoven
Department of Surgery
Erasmus MC Medical Centre Rotterdam

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Koen
Groningen, najaar 2015

Curriculum Vitae

Aaldert Konraad (Koen) Talsma werd geboren op 26 augustus 1980 als jongste van vijf kinderen. Hij groeide op in de omgeving van de Utrechtse Heuvelrug en Gelderse Vallei in Veenendaal. In 1998 begon Koen aan de studie geneeskunde aan de Erasmus Universiteit in Rotterdam. Hij verwierf tijdens zijn studie een Master of Science titel in de Klinische Epidemiologie door een opleiding aan zowel het Netherlands Institute for Health Sciences (NIHES) en de Harvard School of Public Health, Boston VS. Het Rotterdams Bataafsch Genootschap der Proefondervindelijke Wijsbegeerte verleende hem een studieprijs in 2006. Na een senior co-schap Interne Geneeskunde werd hij arts-assistent chirurgie in het Ikazia Ziekenhuis, waar hij begon aan de opleiding tot chirurg in 2007 (opleiders dr. W.F. Weidema and dr. P.T. den Hoed). Overige ziekenhuizen waar Koen werd opgeleid waren: Erasmus MC / Daniel den Hoed (opleiders: prof.dr. J.N.M. IJzermans en dr. B.P.L. Wijnhoven) en het Maasstad Ziekenhuis (opleiders: dr. E.W. van der Harst en dr. R. Klaassen). Tijdens zijn opleidingstijd begon hij aan het promotieonderzoek dat heeft geresulteerd in dit proefschrift onder supervisie van prof.dr.J.J.B. van Lanschot (promotor) en dr. B.P.L.Wijnhoven (copromotor). Nadat Koen in oktober 2013 Koen gecertificeerd gastro-enterologisch chirurg werd, startte hij met het fellowship gastro-intestinale chirurgie in Leeuwarden (2014; MCL-opleider: prof.dr. J.P.E.N. Pierie) en Groningen (2015; UMCG-opleider: dr. K. Havenga). Koen is tevens lid van de hoofdredactie van het Nederlands Tijdschrift voor Heelkunde. Hij is getrouwd met Jobke Thesing en vader van een zoon Sil.

Many improvements have been made in the treatment of oesophageal cancer. Surgical techniques have been refined, multimodality treatment has become the standard of care and nationwide quality audits have been introduced. Nevertheless, there are some persevering challenges in the treatment of oesophageal cancer and its complications: 1. with current staging modalities, even after radical surgery, many patients suffer from early recurrence (“challenge to stage”) ; 2. more than half of the patients who undergo surgery will still die from oesophageal cancer (“challenge to cure”) ; 3. complications after surgery cannot always be treated early and appropriately (“challenge to rescue”) ; 4. surgery alone, without preceding neoadjuvant therapy, too often has the disadvantage of involved surgical resection margins (“challenge to resect”); 5. there is a striking rise in the incidence of oesophageal adenocarcinoma, especially in the Western hemisphere, which is only partly understood (“challenge to prevent”).

This thesis includes clinical studies that address these issues which are still present in treating this devastating disease.

Koen Talsma
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