Identification of risk-factors for perioperative morbidity and mortality during different phases in the treatment of esophageal cancer patients

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Contents

General introduction

Esophageal cancer (EC) belongs to the ten most common cancers in the Netherlands, and accounts for 2.7% of all new cases in men and 1.1% in women[1, 2]. In 2010, approximately 2000 new cases of EC were diagnosed in the Netherlands, an increase of 300% compared to 1989[1, 2]. This is mainly caused by a higher prevalence of patients with gastroesophageal reflux disease (GERD) and Barrett's dysplasia[2, 3]. Barrett's mucosa is a premalignant condition that is almost exclusively related to the formation of adenocarcinoma in the distal one-third of the esophagus[2].

EC is often diagnosed in an advanced stage of the disease with local or systemic spreading of cancer cells. Therefore, many patients are only eligible for palliative treatment with an unfavorable survival rate.

In patients selected on the basis of their overall condition and oncologic stage, a multimodality approach with neoadjuvant chemoradiotherapy (CRT) is currently standard of care in a curative treatment policy[4]. Neoadjuvant CRT improves loco-regional control resulting in an improved resectability and a 5-years survival benefit of 13%. CRT is associated with a pathological complete response (pCR) of the tumor in 15-30% of patients[4, 5]. Nevertheless, surgical resection remains the most important potentially curative treatment, but is associated with substantial perioperative morbidity (40-60%) and in-hospital mortality (3-5%)[6, 7, 8]. Moreover, as many EC patients are above the age of 65 years, they usually present with co-morbidities and may be unfit for surgery.

The goal of the studies included in this thesis, is to identify the most important risk-factors during the various treatment phases in patients with EC who are selected for esophagectomy.

PREOPERATIVE EVALUATION

EC predominantly occurs in the last decades of life; approximately 70% of the newly diagnosed patients were aged 65 years and over[9]. The predisposing factors for the development of EC include smoking, GERD, obesity and alcohol consumption, which are also associated with a range of cardio-pulmonary disorders[9]. Consequently, in these patients a high prevalence of comorbidity exists, for example diabetes mellitus or chronic obstructive pulmonary disease, which can affect treatment outcome[10]. Surgeons will in general be more reluctant to perform major surgery in fragile and elderly patients. Frailty is increasingly used as an important determinant for postoperative outcome and can be defined as the physiologic reserves and resistance to stressors of a patient[11]. In **Chapter 2** the relation between advanced age (i.e. ≥ 70 years), comorbidity and postoperative outcome is evaluated.

Since esophagectomy is associated with considerable postoperative morbidity and mortality, careful preoperative assessment of medical fitness and subsequent selection of appropriate surgical candidates are important steps to improve short-term outcome. Patients with an increased surgical risk and an expected prolonged recovery period might be considered curative radiotherapy or palliative therapy instead, in order to ensure quality of life. So it is pivotal for both the patient and the surgeon to realistically assess the expected impact of the surgical insult. However, reliable individual risk stratifications are still missing in daily practice. One of the most popular models in risk-assessment in surgical literature is the American Society of Anesthesiologists (ASA) score, which is a subjective estimate of organ system disease and preoperative fitness. In **Chapter 3** we evaluated the ASA score and four other frequently used risk-prediction models to examine their ability to predict short-term postoperative outcome.

NEOADJUVANT CRT

The role of neoadjuvant CRT in patients with EC has been debated for decades. Several trials have been published in recent years with conflicting results with regard to long-term survival, but with a growing evidence for a beneficial effect of neoadjuvant CRT[4, 12-14]. In particular, after publication of the CROSS trial, a large national randomized control trial in which our center participated, demonstrated a survival benefit of 13% at 5 years after neoadjuvant CRT[4]. Based on these results and previously published meta-analyses, most centers have chosen for standardization of neoadjuvant CRT in conditionally and oncologically suitable patients. The function of chemotherapy is to enhance the locoregional effect of radiotherapy, which lead to a potentially downsizing of the primary tumor, with improved resectability, and an increased chance to achieve pCR. Chemotherapy might also destroy possible micro-metastases leading to an improved long-term survival.
In contrast to these benefits, neoadjuvant CRT may be accompanied by a subsequently increased risk for adverse events. Commonly known side effects of a temporary nature include nausea, hair loss and neuropathic pain. However, more severe and life-threatening perioperative complications may also occur. Neoadjuvant CRT also seems to be associated with an enhanced risk of developing thromboembolic events (TEE's)[15]. **Chapter 4** evaluates the incidence and impact of preoperative and postoperative TEE's in patients treated with currently used neoadjuvant platinum-based CRT.
It has been reported that a combined therapy of neoadjuvant CRT and subsequent surgery is associated with an increased risk for postoperative cardiopulmonary complications and anastomotic leakage[16]. By adding neoadjuvant CRT to a treatment that already has a considerable effect on the patient's overall condition; concerns have been raised about the impact of neoadjuvant CRT on the postoperative course. Thoracic chemoradiotherapy might increase cardiopulmonary toxicity resulting in increase severity and incidence of

postoperative complications[17, 18]. The objective of **Chapter 5** is to evaluate the effect of CRT on short-term outcomes by comparing the incidence of postoperative complications between patients with and without neoadjuvant CRT.

SURGERY

Patients are considered for curative intended esophagectomy after a complete preoperative workup. Several surgical methods have been well explored, including transhiatal, transthoracic, or minimal invasive esophagectomy. Selection of an appropriate procedure depends on the location of the tumor, patient characteristics and preferences of the surgeon. In general, transhiatal esophagectomy (THE) is associated with a lower rate of (pulmonary) postoperative morbidity, while transthoracic esophagectomy (TTE) can be combined with a two-field lymphadenectomy resulting in improved locoregional control[19]. Compared to THE, TTE is generally accepted as standard procedure, although the pulmonary problems seem to be somewhat higher. The best preventable tool for pulmonary-related problems remains an epidural anesthesia, even in the hands of surgeons who advocated a minimal invasive method. The fact that esophagectomy is technically challenging there is a need of state of the art diagnostic procedures, advanced surgical skills and training. Therefore, performing these surgical resections in is one reason why high volume centers have improved short-term and long-term outcomes[20].

POSTOPERATIVE COMPLICATIONS

In order to minimize the impact of comorbidity on outcome, it is of great importance to identify patients who are at the highest risk of developing a postoperative complication. Since we currently do not possess tools to reliably assess individual risk in daily practice, clinicians have to rely on careful physical examination, and routine postoperative diagnostics such as peripheral blood values. However, the value and degree of abnormal peripheral blood values after esophagectomy and their association with postoperative complications are not fully understood. Consequently, abnormal values after esophagectomy could be expected to be due to malnutrition, comorbidity, the neoplasm itself, age, neoadjuvant therapy, or surgery-related conditions. Identifying patients with postoperative complications based on deranged peripheral blood results is difficult. In **Chapter 6** our aim was to identify the prognostic value of early routine peripheral blood values in predicting short-term outcome after esophagectomy.

IMMUNOLOGICAL RESPONSE

Neoadjuvant CRT and subsequent surgery are both associated with the release of different pro-inflammatory cytokines[21-23]. However, the impact of a combined therapy on patient's immunological response is not clear yet. Prognostic markers to assess the degree of pathological response in EC patients are still missing and could be used as a tool to individualize treatment strategy. Early response evaluation with functional imaging techniques (PET/CT) are promising, but need further validation[24]. It has been suggested that cytokines could reflect the degree of pathological response from neoadjuvant CRT[25, 26]. Patients with pCR might be spared from probably meaningless surgical resection since this severe procedure is not related to improved long-term outcome in these patients[27, 28]. On the other hand, patients without pathological response might have been treated too long with CRT (early response evaluation) and may be planned earlier for definitive surgical resection. Furthermore, cytokine concentrations throughout different phases of treatment seemed to be related to complications caused by either CRT or subsequent surgery. Although, cytokine concentrations have been extensively investigated after esophagectomy, their value in the context of multimodality treatment is far from clear[29, 30]. In **Chapter 7** we analyzed nine different cytokines concentrations during different phases (from start neoadjuvant CRT until the first postoperative week) in the treatment of EC patients to assess the impact on patient's immunological response and to identify for prognostic value on the degree of pathological response after CRT and complications caused by either CRT or subsequent surgery.

AIM OF THE THESIS

Patient characteristics and neoadjuvant CRT might interfere with short-term postoperative outcome. Appropriate selection of candidates for potentially curative treatment options and individualizing treatment strategies are important steps to improve the patient's quality of life. The aim of the thesis is to identify risk-factors contributing to the development of perioperative complications throughout different phases in the treatment of esophageal cancer patients. Early identification of these factors could provide us additional information for a better selection of patients to different curative treatment options.

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Extended esophagectomy in elderly patients with esophageal cancer: Minor effect of age alone in determining the postoperative course and survival

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ABSTRACT

Background: Elderly patients who undergo esophagectomy for cancer often have a high prevalence of co-existing diseases, which may adversely affect their postoperative course. We determine the relation of advanced age (i.e. ≥ 70 years) with outcome and evaluate age as a selection criterion for surgery. Recommendations are given.

Patients and Methods: Between January 1991 and January 2007, we performed a curative intended extended transthoracic esophagectomy in 234 patients with cancer of the esophagus. Patients were divided into two age-groups; < 70 years (group I; 170 pts) and ≥ 70 years (group II; 64 pts).

Results: Both groups were comparable regarding comorbidity (ASA-classification), tumor and surgical characteristics. The overall in hospital mortality rate was 6.2% (5% vs. 11%, p = 0.09). Advanced age was not a prognostic factor for developing postoperative complications (OR = 1.578; 95%CI = 0.857 to 2.904; p = 0.143). The overall number of complications was equal with 58% in group I vs. 69% in group II (p = 0.142). Moreover, the occurrence of complications in elderly patients did not influence survival (p = 0.174). Recurrences developed more in patients < 70 years (58% vs. 42%, p = 0.028). The overall 5-year survival was 35% and when included postoperative mortality 33% in both groups (p = 0.676).The presence of comorbidity was an independent prognostic factor for survival (p = 0.002).

Conclusions: Advanced age (≥ 70 years) has minor influence on postoperative course, recurrent disease and survival in patients who underwent an extended esophagectomy. Age alone is not a prognostic indicator for survival. We propose that a radical resection should not be withheld in elderly patients with limited frailty and comorbidity.

INTRODUCTION

Esophageal cancer predominantly occurs in the last decades of life, with a median age beyond 60 years.(1;2) Although important improvements have been achieved in the multimodality treatment of these tumors, surgery remains the primary curative option.(3;4) Esophagectomy is a high risk procedure with serious postoperative complications and a reported mortality rate ranging from 2 to 6%.(1;3;5) Moreover, esophageal cancer patients often present considerable risk factors for major surgery, including obesity, pulmonary and cardiovascular diseases. (6;7)

Besides the increasing incidence of esophageal adenocarcinoma, the rising life expectancy in the general population is responsible for a relatively large number of elderly patients with esophageal cancer.(1) Elderly patients who undergo esophagectomy often have a high prevalence of comorbidity and frailty, suggesting a negative effect on the outcome and postoperative course. (8-12) Therefore, surgeons are in general more reluctant to perform major surgery in these elderly patients.

There is a lack of evidence regarding the appropriate surgical treatment of esophageal cancer in the elderly population. Some authors propose a transhiatal procedure for better short-term outcome with less morbidity, while others perform a standard extended esophagectomy with a two-field lymphadenectomy in all patients with esophageal carcinoma to achieve maximal oncologic control and minimizing the chance of recurrent disease.(13-15)

In absence of an established definition on elderly patients regarding high risk surgery, most studies defined advanced age as an age ≥ 70 years of age. (8;10;11;16-22)

We report the results from an experienced high volume single center, in elderly patients who underwent an extended transthoracic esophagectomy with a two field lymphadenectomy for cancer of the esophagus. We performed several analyses to determine the effect of advanced age on comorbidity, postoperative course, recurrent disease and survival. We evaluated age as a selection criterion for surgery and make recommendations for the optimal treatment policy in elderly patients.

PATIENTS AND METHODS

Patients characteristics and Treatment

Between January 1991 and January 2007, 234 patients with cancer of the esophagus or gastroesophageal junction (GEJ) underwent esophagectomy with curative intent. All patients underwent surgery in the same high-volume university medical center by the same surgical group, consisting of two surgeons. All included patients were medically fit enough to undergo surgery. Patients who underwent neo-adjuvant treatment in a nationwide trial, starting from 2006 on, were excluded for evaluation to prevent a treatment bias (n = 6). Patients who underwent exploration due to unforeseen extension of disease were excluded.

Comorbidity

Comorbidity was determined by The American Society of Anesthesiologists Physical Status (ASA) classification. ASA is a readily available and widely accepted way to stratify surgical patients according to their perioperative risk and varies between ASA 1 (very good condition) and ASA 5 (moribund patient).(23) ASA class was assigned by the anesthesiologist after completing a structured review of physical status just prior to the esophagectomy.

Preoperative workup

Patients were considered for curative esophagectomy after a complete preoperative workup which included: physical examination, standard laboratory tests, digestive endoscopy, histopathological examination of taken biopsies and detailed preoperative risk assessments. Staging of the tumors was performed by endoscopic ultrasonography (EUS) + fine needle aspiration (FNA) and computed tomography (CT) of the chest, abdomen and cervical region. In all patients newly diagnosed T3-4 or N1 esophageal cancer a ^{18}F-fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET) was performed. In case of anatomical difficulties on PET assessment, a PET/CT fusion was performed. All patients were discussed preoperatively in multidisciplinary meetings.

Surgery

An extended esophageal resection was performed in all patients. This procedure consisted of a subtotal esophageal resection through a left thoraco-laparotomy with intrathoracic anastomoses for the distal and gastroesophageal cancers or through a right thoraco-mid laparotomy with cervical anastomoses for the higher intrathoracic tumors. Both were combined with a two-field lymphadenectomy of nodes at the celiac trunk, upper border of the pancreas, para-aortic region and mediastinal nodes.

Histology

All resected specimens and lymph nodes were examined according to the standard procedures. Tumor stage and grade were classified according to the sixth edition of the tumor-node-metastasis system and the residual tumor (R) classification of the International Union Against Cancer and the American Joint Committee on Cancer. (24;25) Adenocarcinomas seen on H&E staining were confirmed in all cases by keratin staining (immunohistochemic analysis).

Mortality and Complications

Postoperative mortality was defined as any death within the first 90 days after operation and deaths within the same hospital admission. A separate calculation was made of only 90 days mortality (without in hospital deaths after 90 days) to compare these figures with the data in literature. Major complications were divided into pulmonary complications: respiratory insufficiency (prolonged need for mechanical ventilation), acute respiratory distress syndrome (ARDS: acute and persistent lung inflammation with increased vascular permeability and severe hypoxemia), pneumonia (infiltrate on X-ray, sepsis and positive sputum culture, including bronchoaveolar lavage), atelectasis (collapse of lung lobe on X-ray with hypoxemia for which intensive physiotherapy or bronchoscopy was needed), pleural effusion (fluid seen on X-ray for which drainage was necessary because of hypoxemia), empyema (positive culture or positive fluid) and pulmonary embolism (diagnosed on CT); Cardiac complications; arrhythmia (diagnosed on ECG) and myocardial infarction (diagnosed on ECG and positive laboratory tests); and other major complications; re-bleeding (bleeding requiring transfusion or reoperation), subphrenic abscess and/or intra-abdominal abscess (CT, drainage and positive culture), Systemic inflammatory response syndrome (SIRS: deregulated host with inflammatory response whit absent infection: temperature > 38.5 °C or < 35 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg and white blood cells > 12,000 cells/mm3), sepsis (the clinical signs of SIRS, but with culture-proven infection or an infection identified by visual inspection), anastomotic leakage (CT with enteral contrast and amylase in the pleural fluid), chylothorax (chyle defined by measuring triglycerides), renal failure (rising creatinine and oliguria for which renal replacement therapy was necessary), liver failure (rising bilirubin, liver enzymes, lactate and prothrombin time), deep venous thrombosis (of the distal or proximal lower extremity) and ileus (absence of peristalsis with gastric retention and no defecation, confirmed with abdominal X-ray). Minor complications were defined as wound infections (positive wound culture with pus), wound dehiscence (spontaneous opening of the fascia) and urinary tract infections (UTI: sepsis, urinary leucocytes and 10^5 bacteria/ml in the urine). Infectious complications were subdivided in septic complications (sepsis), intra-abdominal or subphrenic abscess eventually with anastomotic leakage, empyema, pneumonia, severe wound infections and urinary tract infections. The use of antibiotics and inotropes was scored during the postoperative period. The operation room (OR) time, intensive care unit (ICU) stay and hospital stay were measured for comparison.

Follow-up

All medical follow-up data was collected prospectively, in a patient research database. Patients were seen in the outpatient department every 3 months for the first postoperative year, every 6 months for the next year and then annually for ten years. Data of deceased

patients was collected by consulting the general practitioners and the Comprehensive Cancer Center North Netherlands. Follow-up was measured in months from the time of operation until death (survival time) or end of follow-up with a minimum of two years.
For the calculation of long term cancer specific survival, patients without postoperative mortality were selected (n = 219) and only cancer related death cause was scored. Death of any other cause was scored as end of follow up. For all other survival calculations postoperative mortality was included into the survival curves.
Recurrent disease was defined as loco-regional recurrence or distant metastases in the follow-up period, determined by any cytologic or histologic proof, unequivocal radiologic suspicion (CT, MRI, PET, bone-scan and Ultrasonography) and/or obvious clinical manifestations.
The follow-up was ascertained in February 2009, and complete for all included patients.

Definitions and Statistical Analysis

For calculations 'the elderly' were defined as patient of 70 years of age and older, as generally used in literature. (8;10;11;16-22) Therefore, we discriminated between group I, < 70 years and group II, ≥ 70 years of age, independently of other factors.
Variables were reflected as frequencies with means and/or median with percentages. Continuous variables were compared by using the T-test and the Chi-Square test was used for comparison of categorical variables. Survival and recurrence rates were calculated by the Kaplan-Meier method and the log rank test. Survival calculations included postoperative mortality, except for the cancer specific survival. Prognostic factors for survival were calculated with Cox regression univariate and multivariate analyses. Univariate and multivariate logistic and linear regression analysis were used for calculating if advanced age was influencing the occurrence of comorbidity and complications; group of complications (cardiac, pulmonary and infectious complications) were calculated as well as the individual complications. Multivariate analysis was performed by incorporating factors as covariates with a p-value ≤ 0.1 on univariate analysis.
For all calculations a p-value of < 0.05 was considered to be significant. Statistical computations and figuring were all performed by using the statistical package SPSS version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

The study population consisted of 234 consecutive patients; 196 males (84%) and 38 females (16%). The mean age at operation was 63 years with a range from 28 to 82 years

Table 1. Patients and tumor characteristics (n = 234)

Variable	< 70 years N = 170	≥ 70 years N = 64	P Value
Mean age	58.9	74.5	
Sex (M/F)	144/26	52/12	0.524
Histology			
Adenocarcinoma	145 (85)	56 (87)	
Squamous cell carcinoma	25 (15)	8 (13)	0.666
Localisation			
Midesophagus	14 (8)	4 (6)	
Distal esophagus	102 (60)	36 (56)	
GEJ	54 (32)	24 (38)	0.371
Tumor stage			
I	17 (10)	11 (17)	
IIa	46 (27)	17 (26)	
IIb	16 (9)	8 (13)	
III	80 (47)	25 (39)	
IVa	11 (7)	3 (5)	0.148
Comorbidity			
Diabetes Mellitus	17 (10)	8 (13)	0.582
Hypertension	28 (16)	15 (23)	0.221
Angina pectoris	12 (7)	5 (8)	0.843
Heart failure	1 (1)	2 (3)	0.125
Myocardial infarction	17 (10)	7 (11)	0.833
COPD	16 (9)	6 (9)	0.993
TIA/CVA	7 (4)	6 (9)	0.118

of age. Group I (< 70 years of age) consisted of 170 patients (73%) and group II (≥ 70 years of age) of 64 patients (27%). Patients and tumor characteristics are summarized in table 1. Surgical characteristics such as year of surgery (p = 0.4) and type of resection (p = 0.9) were similar in both groups. Stage of disease was not statistically different in both groups (p = 0.148) although more advanced disease seems to occur in the younger patients (Table 1)

Comorbidity was not significantly different in both groups, respectively 65 patients (38%) with comorbidity in group I versus 32 patients (50%) in group II (p = 0.104). ASA scores did not differ between the two groups (p = 0.136).

Mortality and comorbidity

Postoperative mortality (90 days and within hospital admission) was 6.2% (15 patients), 8 patients (5%) in group I versus 7 patients (11%) in group II (p = 0.09). The 90 days mortality alone was 4,7% (11 patients), 5 patients (3%) in group I and 6 patients (9%)

in group II (p = 0.08). Of the 15 patients who died postoperatively, 10 (67%) had more than one comorbidity (p = 0.041). Four patients had a history of myocardial infarction and hypertension; one patient had diabetes with myocardial infarction; two patients had diabetes with hypertension; one patient had chronic obstructive pulmonary disease (COPD) with transient ischemic attack (TIA), and two patients had a TIA with hypertension. Only cardiovascular comorbidity in the elderly subgroup (n = 24; 38%) had a negative effect on postoperative mortality (p = 0.043).

Complications

Ninety-nine patients (58%) in group I and 44 patients (69%) in group II developed postoperative complications, which was not statistically different between both groups (p = 0.142). Pulmonary complications occurred in 72 patients (42%) in group I versus 36 patients (56%; p = 0.06) in group II, respectively. (Table 2) Respiratory insufficiency was the most frequent complication, and occurred more in the elderly patients (25% versus 41%; p = 0.017). Other major pulmonary complications atelectasis (14% vs. 28%; p = 0.009) and pleural effusion (15% vs. 27%; p = 0.036) occurred more frequent in group II. Cardiac complications, primarily consisting of arrhythmias, occurred in 27 patients (16%) versus 24 patients (38%) in group II (p = 0.001). Pneumonia was the most common infectious complication in 43 patients (18%), 16% in group I and 23% in group II (p = 0.221). There were no differences between infectious and non-infectious complications between the two groups (p = 0.5). Four abscesses developed in the elderly group (6%).

The postoperative use of antibiotics and inotropes did not differ statistically between both age groups (p = 0.4 and p = 0.13).

In logistic regression analysis, age ≥ 70 years was no prognostic factor for development of postoperative complications (Odd Ratio; OR = 1.578; 95% confidence interval; 95%CI = 0.857 to 2.904; p = 0.143). For cardiac complications (OR = 3.178; 95%CI = 1.655 to 6.100; p = 0.001) and pulmonary complications (OR = 1.750; 95%CI = 0.980 to 3.126; p = 0.05) as a group, age ≥ 70 years was a prognostic factor. (Table 3)

There was a higher rate of complications in the patients with comorbidity; 69 of the 97 patients who had comorbidity (71%) developed one or multiple postoperative complications (p = 0.008). However, of the 143 patients who had complications only 69 (48%) had preoperative fixed comorbidity. In logistic regression analysis comorbidity was a prognostic factor for developing postoperative complications (OR = 2.098, 95%CI = 1.207 to 3.647, p = 0.009)

Postoperative course

The operation time with a median of 6 hours was not different in both groups (95%CI = −0.72 to 0.28; p = 0.384). The median ICU stay was 3 days with a range from 1 to

Table 2. Complications (n = 234)

Variable	Group 1 (< 70) N = 170	Group II (≥ 70) N = 64	P-value
Overall complications	99 (58)	44 (69)	0.142
Pulmonary complications	72 (42)	36 (56)	0.058
Respiratory insufficiency	42 (25)	26 (41)	**0.017**
ARDS	4 (2)	3 (5)	0.351
Pneumonia	28 (16)	15 (23)	0.221
Atelectasis	23 (14)	18 (28)	**0.009**
Pleural effusion	25 (15)	17 (27)	**0.036**
Empyema	16 (9)	9 (14)	0.306
Pulmonary embolism	4 (2)	3 (5)	0.351
Cardiac complications	27 (16)	24 (38)	**< 0.001**
Arrhythmia	27 (16)	23 (36)	**0.001**
Myocardial infarction	2 (1)	1 (2)	0.815
Other major complications			
Rebleeding	4 (2)	4 (6)	0.144
Subphrenic abcess	0 (0)	2 (3)	**0.021**
SIRS	3 (2)	4 (6)	0.073
Sepsis	14 (8)	9 (14)	0.183
Anastomotic leakage	31 (18)	8 (13)	0.295
Chylothorax	9 (5)	2 (3)	0.486
Intra-abdominal abces	0 (0)	2 (3)	**0.021**
Renal failure	8 (5)	5 (8)	0.356
Liver failure	0 (0)	1 (2)	0.103
Deep venous thromb	2 (1)	0 (0)	0.385
Ileus	2 (1)	2 (3	0.306
Minor complications			
Wound infection	9 (5)	9 (14)	**0.025**
Wound dehiscence	3 (2)	2 (3)	0.522
Urinary tract infection	0 (0)	4 (6)	**0.001**
Postoperative course			
Reoperation	17 (10)	12 (19)	0.064
OR-time (mean hours)	6.1	6.3	0.384
ICU stay (mean days)	2.5	5.0	**< 0.001**
Hospital stay (mean days)	21.0	27.0	**0.014**

64 days. In group II the ICU stay was significantly longer with a median of 7 days (range 1 to 64 days) versus group I with a median of 3 days (range 1 to 56 days) (95%CI = −9.95 to −1.86; p = 0.005). Re-operation was needed in 29 patients due to complications, including anastomotic leakage, postoperative bleeding, subphrenic abscess and obstructive ileus based on torsion at the jejunostomy site. The median hospital stay was 22 days, with 21 days in group I and 26 days in group II (95%CI = −11.03 to 0.17; p = 0.06).

Table 3. Prognostic value of advanced age on development of complications; with group of complications (overall, pulmonary and cardiac complications) and individual complications. np = not enough statistical power.

Variable	Odds ratio	95%CI	P-value
Overall complications	1.578	0.857 - 2.904	0.143
Pulmonary complications	1.750	0.980 - 3.126	**0.050**
Respiratory insufficiency	2.085	1.135 - 3.832	**0.018**
ARDS	2.041	0.444 - 9.383	0.359
Pneumonia	1.552	0.766 - 3.146	0.222
Atelectasis	2.501	1.242 - 5.037	**0.010**
Pleural effusion	2.098	1.043 - 4.218	**0.038**
Empyema	1.575	0.658 - 3.770	0.308
Pulmonary embolism	2.041	0.444 - 9.383	0.359
Cardiac complications	3.178	1.655 - 6.100	**0.001**
Arrhythmia	2.971	1.542 - 5.723	**0.001**
Myocardial infarction	1.333	0.119 - 14.962	0.816
Other major complications			
Rebleeding	2.767	0.671 - 11.412	0.159
Subphrenic abcess			np
SIRS	3.711	0.807 - 17.066	0.092
Sepsis	1.823	0.747 - 4.449	0.187
Anastomotic leakage	0.641	0.277 - 1.479	0.297
Chylothorax	0.577	0.121 - 2.746	0.490
Intra-abdominal abces			np
Renal failure	1.716	0.540 - 5.455	0.360
Liver failure			np
Deep venous thromb			np
Ileus	2.710	0.374 - 19.655	0.324
Minor complications			
Wound infection	2.927	1.106 - 7.748	**0.031**
Wound dehiscence	1.796	0.293 - 11.003	0.527
Urinary tract infection			np

Long term outcome

Median follow-up was 26 months (range 0–199 months) and no patients were lost to follow-up. Follow-up time was not different between the groups (p = 0.701).

Stage of disease had no impact on survival between the two groups (stage I, p = 0.298; stage II; p = 0.834; stage III; p = 0.184; stage IVa; p = 2.09).

None of the individual complications had a significant impact on survival. Overall, complications had no influence on both the long term survival including postoperative mortality (p = 0.174) and without mortality (p = 0.655).

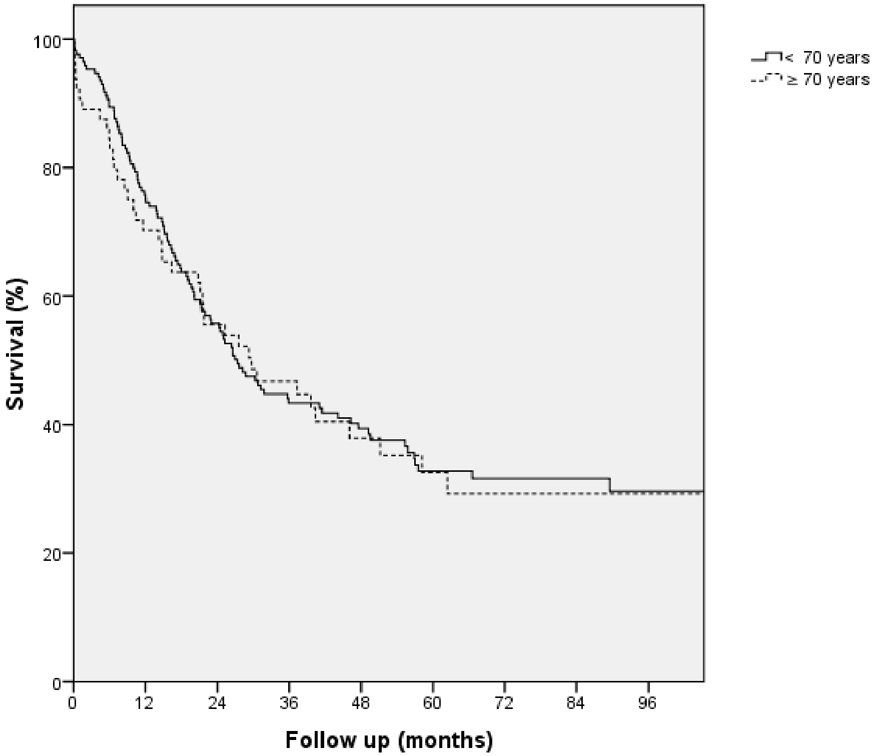

Figure 1. Kaplan Meier overall survival curve (n = 234) of patients in group I, < 70 years and group II, ≥ 70 years of age (n = 170 versus n = 64, p = 0.535), including postoperative mortality.

Recurrent disease occurred in 126 patients (54%); 99 patients (58%) in group I and 27 (42%) in group II (p = 0.028). Time to development of recurrent disease did not differ between the groups (p = 0.223).

For all 234 patients, including patients with postoperative mortality, the 1-year survival was 74% and the 5-year survival was 33%. There was no difference in survival between the two groups (p = 0.535), with a 1-year survival of 76% in group 1 versus 70% in group 2 (p = 0.282) and a 5-year survival of 33% in group I versus 33% in group II (p = 0.676). (Figure 1)

Age classification in < 70 and ≥ 70 years of age did not have any prognostic value for survival (OR = 1.117, 95%CI = 0.787 to 1.584; p = 0.535). Also a rising age as continuous variable did not have a prognostic value for worse survival (OR = 1.005, 95%CI = 0.990 to 1.021; p = 0.514).

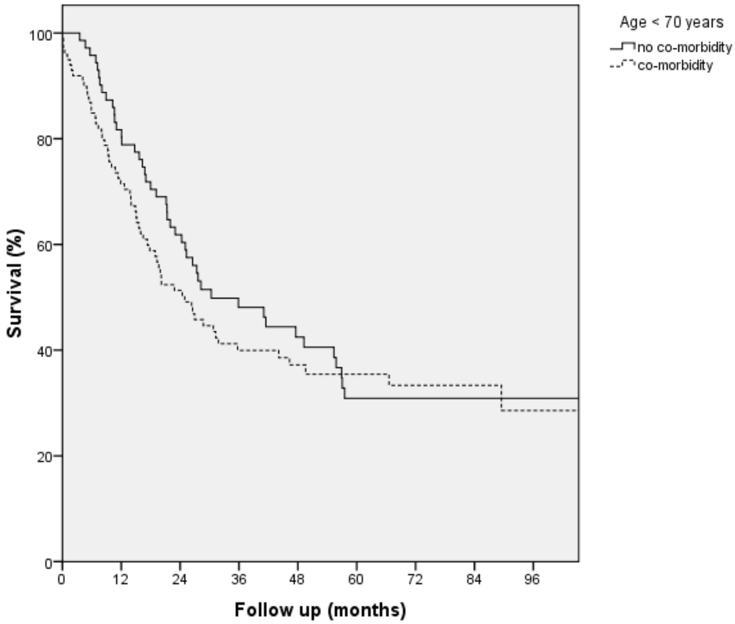

Figure 2A. Kaplan Meier survival curve of patients in group I (< 70 years) with preoperative comorbidity and those without (n = 65 versus n = 105, p = 0.472).

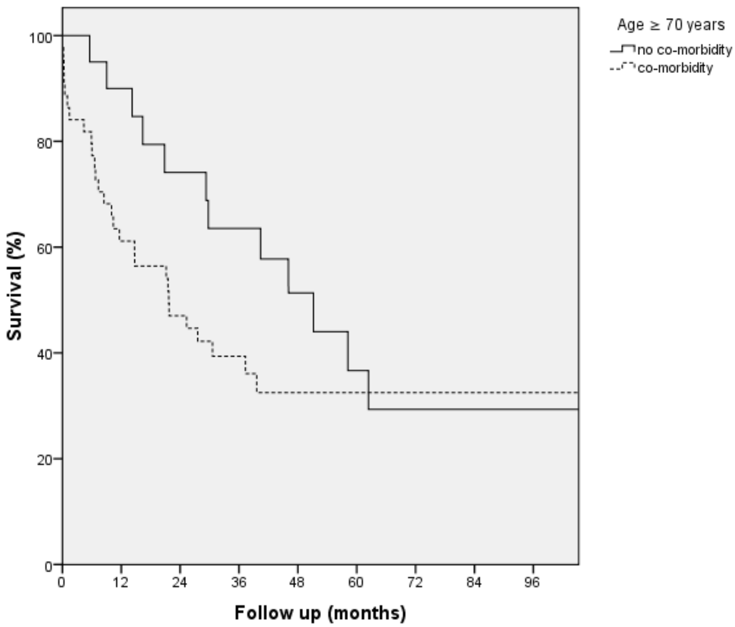

Figure 2B. Kaplan Meier survival curve of patients in group II (≥ 70 years) with preoperative comorbidity and those without (n = 32 versus n = 32, p = 0.087).

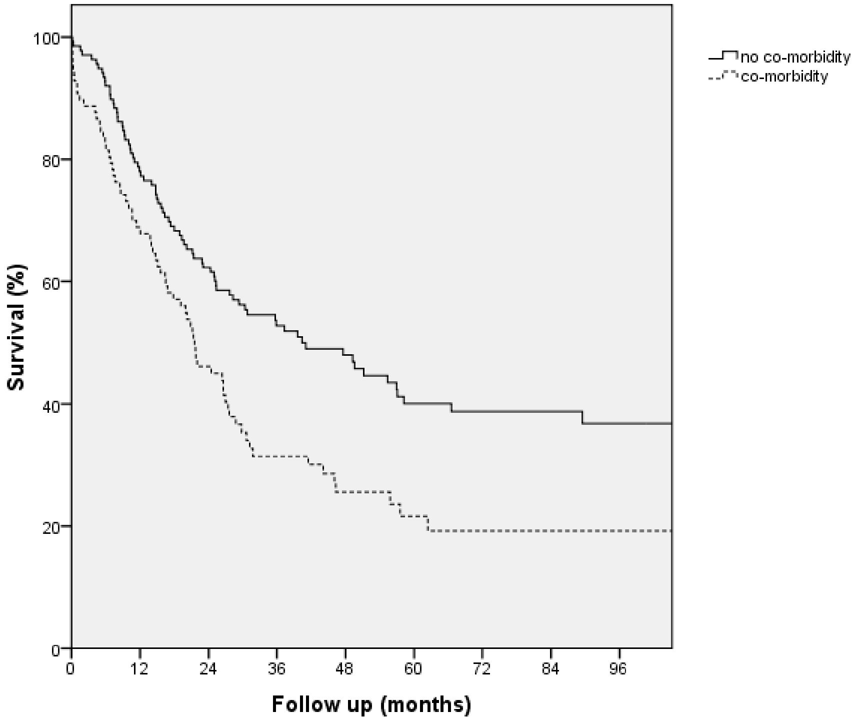

Figure 3. Kaplan Meier survival curve of patients with preoperative comorbidity and those without, regardless of age (n = 97 versus n = 137, p = 0.001).

Cancer related 5-year survival, in patients without postoperative mortality (n = 219) and cancer related cause of death, was 35% and did not differ between the groups (35% versus 37%, p = 0.874).

Survival curves of comorbidity versus age showed no difference between the two groups (p = 0.135). In group I and II separately, there was no statistical difference in survival of patients with and without comorbidity. (Figure 2A and 2B) Although there was a trend for worse survival in elderly patients with comorbidity (p = 0.087). (Figure 2B)

The presence of comorbidity was an independent prognostic factor for long term survival (OR = 1.679 95%CI = 1.219 to 2.314; p = 0.002. The Kaplan Meier curve showed significant better survival for patients without comorbidity in the long term (p = 0.001). (Figure 3).

DISCUSSION

By applying a thoracotomy-based operative approach with extensive 2-field lymph node dissection for esophageal cancer, we were able to effectuate a 5-year cancer specific survival rate of 35% in a patient population with 49% stage III and IV disease, regardless of age and comorbidity.

The median hospital stay was comparable with reported numbers in literature. (12) Hospital stay is relative long because some patients with comorbidity in this relatively high-aged population needed extensive pre-operative workup. Moreover, in our hospital most patients with anastomotic leakage are usually treated conservatively with good results.

Advanced age (≥ 70 years) had no significant influence on mortality following extended esophagectomy, even though there was a non-statistical trend of a higher postoperative mortality. Overall, elderly patients had no higher postoperative complication rate than the younger group. However, cardiac complications in particular arrhythmia, and pulmonary complications, especially respiratory insufficiency, atelectasis and pleural effusion, occurred more frequently in the elderly patients. Age ≥ 70 years was not a prognostic factor for development of postoperative complications. Furthermore, the occurrence of complications did not lead to a decreased survival. On the other hand comorbidity was the strongest prognostic factor for the development of complications. In this study cardiovascular comorbidity in the elderly subgroup had a negative effect on postoperative mortality. Because of this relatively small sized subgroup, it is difficult to give specific recommendations.

Compared with patients < 70 years recurrent disease was significant lower in the elderly group. But the higher number of cardiopulmonary complications and the trend for a higher postoperative mortality in the elderly is concerning.

Along with a general rise of incidence of esophageal adenocarcinoma, there is a rising incidence in esophageal cancer in the elderly patients up to 600% in the last decades.(26) Advances in treatment of esophageal cancer surgery have been remarkable; improved staging modalities, perioperative management, surgical techniques and postoperative care have reduced postoperative mortality and morbidity rates and enhanced better survival. Moreover, improvements in postoperative complications in the elderly are reported.(19)

Our results reflect the improvement in overall outcomes following esophagectomy for cancer over the last ten years and demonstrate that this improvement in short-term outcome is evident in the elderly population.(20) Several studies reported worse postoperative course in the elderly patients, with a high mortality rate and a decreased overall long term survival with increasing age.(20;22) More recent studies showed acceptable results regarding mortality and survival because of better surgical techniques, centralization and more intensive perioperative care.(8;10-12;16-19;21;27) Therefore, some studies focus on even older patients (> 75 or > 80 years). (9;12;16).

Preoperative risk assessment and estimation of prognostic risk factors in the elderly remain controversial. Some studies found a strong association between high age and increased risk of worse prognosis during and after esophagectomy.(7;28) Particularly cardiac and pulmonary complications occur more frequently in the high age groups.(8;16;19;28) However, reliable individual risk analysis stratification for individual elderly patients is lacking. This is mainly due to a reluctance to enroll elderly patients in clinical trials, which we think is not appropriate.(29) This is of importance, because the elderly have more cardiopulmonary complications which complicate the postoperative course. More research is needed for adequate scoring systems identifying the elderly at risk for pulmonary and cardiac complications.(8;16;19;28) This may permit preoperative intervention such as cardiac and pulmonary support which can reduce the risk of postoperative complications.(12)

In the literature, a discussion is ongoing on the type of surgery required for elderly patients. Some surgeons advocate a limited resection due to postoperative complications and co-existing disease in the elderly. However, transthoracic esophagectomy with two-field lymph node dissection is not associated with increased mortality or reduced long term survival in the elderly population.(20) In this study there was a higher mortality rate in the elderly, although not significant, but elderly patients had an equally long term survival after surgery. Further optimization in selection criteria and risk stratification for the elderly will better clarify the supposed advantage of extended esophagectomy. Hence we recommend thorough preoperative assessment in all patients. A threshold to deny surgery based only on age seems not reasonable in this patient group, because of large differences in comorbidity and clinical manifestations of cancer.

A larger study group might strengthen the non-statistical trends on postoperative mortality in this study, suggesting the need for a large prospective study. The choice to operate on elderly patients with comorbidity remains difficult, but the consequences to not operate is even a greater dilemma. The strength of this study is the careful selection of patients for surgery, the homogeneous groups for comparison and the complete follow up. It quantifies what the risk is in an experienced center.

More attention is needed in prospective clinical trials for elderly patients, further improving postoperative course and long term survival. Furthermore, individual risk analysis stratification should be developed with a focus on patients with comorbidity. Centralization and more intensive perioperative care for elderly patients are mandatory. Our data support the view that esophageal resection within centralized organized care with a coordinated multidisciplinary approach and multidisciplinary teamwork is feasible and appropriate for all reasonably fit patients, regardless of age. The increased use of neo-adjuvant therapy in the elderly patients is needed, especially in clinical trials, with the perception that

individualization of treatment will be the future standard. A subdivision based solely on age is undesirable. Elderly patients with no preoperative risk factors may be more readily tolerate chemo-radiotherapy and surgery than younger patients with comorbidity.
In conclusion, the increasing life expectancy in the general population will lead to a further increasing incidence of elderly patients with esophageal cancer in the near future. Therefore more attention is needed for the treatment of the elderly patients. As this study showed no significant difference in short and long term survival for the elderly group, and elderly patients had no substantial worse postoperative course, a radical resection should not be withheld in the elderly patients. Although, age alone is not a prognostic indicator for survival in patients who undergo an esophagectomy for cancer, co morbidity at any age might be.

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2

Comparison of different risk-adjustment models in assessing short term surgical outcome following transthoracic esophagectomy in patients with esophageal cancer

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ABSTRACT

Background: Different risk-prediction models have been developed, but none is generally accepted in selecting patients for esophagectomy. This study evaluated five most frequently used risk-prediction models, including the American Society of Anaesthesiologists (ASA), P-POSSUM, O-POSSUM, Charlson and its age adjusted score (ACCI) to asses postoperative mortality after transthoracic esophagectomy.

Methods: Data were obtained from 278 consecutive esophageal cancer patients between 1991 and 2007. Performance in predicting postoperative mortality (in-hospital and 90-day mortality), were analyzed regarding calibration (Hosmer and Lemeshow goodness-of-fit (HLG) test) and discrimination (area under the Receiver Operator Curve (ROC)).

Results: The HLG test was applied to each model and showed a significant outcome for only the P-POSSUM score (p = 0.035). The ROC curve indicated discriminatory power for P-POSSUM (0.766) and for O-POSSUM (0.756) other models didn't exceed the minimal surface of 0.7.

Conclusion: Postoperative mortality after esophagectomy was best predicted by O-POSSUM. However, it still over-predicted postoperative mortality.

INTRODUCTION

Esophageal cancer is associated with high rates of perioperative morbidity and mortality and a relatively low overall 5-year survival rate of approximately 25% [1]. The incidence is increasing rapidly and appears to be most prominent in vulnerable and fragile elderly of > 70 years who withstand major surgical insult as well[2]. Unfortunately, many elderly patients have serious comorbidities interfering with the outcome of treatment [3,4]. Careful preoperative assessment of fitness and subsequent selection of appropriate surgical candidates are important steps improving short-term outcome for individuals who undergo an esophagectomy.

New standard treatment methods, including neo-adjuvant chemoradiotherapy with reported complete responses of 20-40% after resection, can be performed safely in a great part of these patients[5]. Nevertheless, surgery remains the primary curative option[6,7]. However, esophagectomy as a high-risk complex surgical procedure has a severe postoperative complication rate of up to 50% with a relatively high postoperative mortality of around 5% and in some cohorts even approaching 10-15% [6,8,9].

Preoperative risk stratification for postoperative mortality may help patients and families address the magnitude of both the disease and the therapy. It is pivotal for both the patient and the surgeon to realistically assess the magnitude of the surgical insult. Therefore we propose to assess several preoperative scoring systems that have each been validated as predictive of severe postoperative morbidity and mortality[10-14].

These “risk stratification/adjustment systems” include the “Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity” (POSSUM), its Portsmouth (P-POSSUM) and O-POSSUM modifications, the Charlson Comorbidity Index (CCI) with the version of Age Adjusted Charlson Score (ACCI) and the standard American Society of Anesthesiologists (ASA) classification systems. In most of these systems age is not included as a dominant predictor of morbidity that is uniquely relevant to esophageal cancer presenting nowadays in more aging patients.[14]. Until now there are no published studies comparing all these five comorbidity models (P- and O-POSSUM, Charlson-, ACCI- and ASA score) for patients after esophagectomy. We examined which of these five most frequently used comorbidity models could predict short-term surgical outcomes accurately following curatively intended resection in esophageal cancer patients.

PATIENTS AND METHODS

Patient's characteristics

Between January 1991 and December 2007, 280 consecutive patients with cancer of the esophagus underwent a surgical resection with curative intent. Two patients with missing follow-up were excluded from the analysis. In the remaining group of 278 patients analysis was performed based on prospectively registered data from a computerized database of all esophageal procedures at our university hospital. (Table 1) Data of this study were evaluated according to the rules of ethical board of our institute. There were no systemic changes over the study period in the methods of acquiring patient comorbidity data.

Preoperative work up

Preoperative evaluation consisted of physical examination, standard laboratory tests and detailed preoperative risk assessments. Staging was performed by endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) of suspected lesions and 16-64 slice multidetector computed tomography (MDCT) of the chest, abdomen and cervical region. From 1996 on all patients diagnosed as T3-4 or N1 were additionally staged with ^{18}F-fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET) and PET/CT fusion was applied in case of anatomical difficulties on PET assessment. Since 2007 neo-adjuvant chemoradiotherapy consisting of paclitaxel 50mg/m^2 and carboplatin (AUC = 2) on day 1,8,15,22 and 29 with concurrent radiotherapy of 41.4 Gy (23 fractions of 1.8 Gy), was administered to ten patients, as a part of a randomized control trial with surgery alone.

Surgery

Surgery in our tertiary referral centre was performed by two experienced surgeons. All patients underwent a curative intended open radical transthoracic esophagectomy consisting of a subtotal esophageal resection including a two-field lymphadenectomy of nodes at the celiac trunk, along the upper border of the pancreas, para-aortic region and mediastinal nodes. Pathological staging was based according to the latest edition of the TNM classification for esophageal cancer[15].

Comorbidity and mortality indexes

Overall comorbidity severity was classified according to the modified Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM and O-POSSUM), Charlson-, Age Adjusted Charlson- and ASA score.
The original POSSUM score overpredicted mortality in low-risk patients[16] and therefore transformed into the Portsmouth predictor equation (P-POSSUM), with a different logistic

Table 1. Variables of P-POSSUM and O-POSSUM

Physiological score	Operative severity score
Age (years)	Operative severity
Glasgow coma score	Multiple procedures
Cardiac signs	Total blood loss *
Respiratory signs	Peritoneal soiling *
Electrocardiography	Presence of malignancy *
Systolic pressure (mmHg)	Mode of surgery
Pulse rate (beats/min)	
Haemoglobin (g/dl)	
White blood cell count ($x10^{12}$/L)	
Urea (mmol/L)	
Sodium (mmol/L)	
Potassium (mmol/L)	

* only in P-POSSUM

regression. Both risk prediction models are based on a preoperatively available 12-factor physiological score and a 6-factor operative severity score obtained after surgery. To provide in the need for a specialized risk prediction model for esophagogastric surgery, the adapted O-POSSUM equation was designed[17] (Table 1).

The nineteen conditions of the Charlson comorbidity index (CCI) were found to significantly influence survival and were given a weighted, risk-adjusted comorbidity index value, varying from 1 to 6 points, for the individual patient[18]. Patients with a low score were considered to have minimal co-morbid diseases in their medical history. In our study we used the modification by Romano et al[19], as it excludes cancer diagnosis in determining comorbidity and is commonly used in cancer outcomes research. The Charlson comorbidity index reflects both the number and gravity of co-morbid diseases. Besides the Charlson score, we also used the Age Adjusted Charlson Index (ACCI) scorings system, which characterized the impact of age and comorbidity on disease progression and survival after surgery[20]. Both models were initially developed for administrative databases and not for individual patient level data sets. The commonly used American Society of Anesthesiologists Physical Status (ASA) classification is a readily available and widely accepted to stratify surgical patients according to their perioperative risk. It varies from ASA 1 (normal healthy patient in good condition) to ASA 5 (moribund patient, not expected to survive) [21]. ASA class is assigned by the attending anaesthesiologist after completing a structured review of physical status just prior to the patient's surgical procedure. Although the ASA classification was initially not intended to predict survival beyond the perioperative period, several investigators demonstrated a prognostic value for the ASA classification beyond this period[21].

Statistical analysis

The primary outcome was postoperative mortality, hereby defined as death within 90 days after esophagectomy or any death during admission in hospital where the resection was performed. This time period was applied to include all operation-related deceased patients. The observed number of deceased patients was divided by the number of expected deceased patients (O/E) and gave a standard mortality ratio (SMR). The performance of P- and O-POSSUM, Charlson-, ACCI- and the ASA score in predicting postoperative mortality was analysed regarding calibration and discrimination. Calibration refers to the agreement between observed outcomes and predicted probabilities and concerns the expected mortality rate for a group of patients. Comparison between observed and expected (O-E) deaths for each model was analysed with the Hosmer and Lemeshow (HL) goodness-of-fit test. [22,23] Higher values of the HL statistic represent poorer model calibration. In this analysis a value of $P < 0.05$ was considered to show a statistically significant lack of fit. Discrimination refers to the ability to distinguish patients who will die from those who will survive by computing the area under the receiver operating characteristic (ROC) curve (AUC). Values between 0.7-0.8 suggest reasonable or moderate discrimination and values exceeding 0.8 suggest good or excellent discrimination.

For a better applicability in clinical practice, both POSSUM models were divided into three risk categories: group I (low risk) with a postoperative mortality rate: 0 – < 8%; group II (intermediate risk): 8 – < 15% and group III (high risk): ≥ 15 – 100% [24].

To counteract the possibility of changes in hidden care over the study period (1991-2007) of time we divided this period in three segments. The predictive powers of these models were analyzed in each time segment and were compared with the overall predictive power. All statistical analyses were conducted by the statistical software SPSS 16.0.2 (SPSS Inc., Chicago IL, USA).

RESULTS

Clinicopathologic characteristics of the patients are summarized in Table 2. The 90-day postoperative mortality was 6.5% (18 patients), including an in-hospital mortality of 5.4% (n = 15). The overall comorbidity severity evaluated according to the five most commonly used models was as follows.

Evaluation of the POSSUM equation

The expected mortality ratio by P-POSSUM was 6.2% (17 patients) giving a standardized mortality ratio (SMR) of 1.05 (18/17). O-POSSUM expected a postoperative mortality rate of 9.7% (27 patients), which leads to a standard mortality ratio (SMR) of 0.67 (18/27). This

Table 2. Patient (N = 278) and tumor characteristics according to postoperative outcome.

	Postoperative survivors (N = 260) (%)	**Postoperative deceased patients (N = 18) (%)**
Median age (years) (range)	63 (29-85)	70 (55-81)
Sex (M/F)	214 / 46 (82.3/17.7)	15 / 3 (83.3/16.7)
Histology		
Adenocarcinoma	218 (83.9)	17 (94.4)
Squamous cell carcinoma	42 (16.2)	1 (5.6)
Localization		
Midesophageal	22 (8.5)	1 (5.5)
Distal esophagus	238 (91.5)	16 (94.5)
Tumor stage		
I	38 (14.7)	1 (5.6)
IIa	68 (26.2)	2 (11.1)
IIb	34 (13.1)	0 (0.0)
III	107 (41.2)	14 (77.8)
Iva	13 (5.0)	1 (5.6)

value indicates an overestimation by O-POSSUM. The risk classification of both POSSUM models, with subdivision in observed (O) and expected (E) mortality rates, are summarized by Table 3.

Calibration of the Hosmer and Lemeshow statistic demonstrated no fit to the observed data for P-POSSUM ($\chi^2 = 16.580$, 8df (degrees of freedom), p = 0.035), in contrast to the calibration of O-POSSUM ($\chi^2 = 7.074$, 8df, p = 0.529; Table 4). The area under the ROC curve for P-POSSUM was 0.766 (95% confidence interval (C.I) 0.67 to 0.86; p = 0.000),

Table 3. Outcomes of P-POSSUM and O-POSSUM stratified for risk groups: observed and expected mortality rates

P-POSSUM Score (%)*	Patients (N)	Observed mortality % (N)	Expected mortality % (N)
0 – < 8	219	3.7% (8)	3.5% (8)
8 – < 15	41	12.2% (5)	10.6% (4)
≥ 15 – 100	18	27.8% (5)	29.1% (5)
Total	278	6.5% (18)	6.2% (17)
O-POSSUM Score (%)*			
0 – < 8	137	1.5% (2)	4.8% (7)
8 – < 15	97	9.3% (9)	11.4% (11)
≥ 15 – 100	44	15.9% (7)	20.8% (9)
Total	278	6.5% (18)	9.7% (27)

*Possum Risk Group

Table 4. The five risk-adjustment models: calibration and discrimination

Risk-prediction Model	Hosmer and Lemeshow test (p)	Area under the ROC curve (95% CI)
P-POSSUM	0.035	*0.766* (0.67 – 0.86)
O-POSSUM	*0.529*	*0.756* (0.67 – 0.84)
Charlson score	*0.659*	0.567 (0.42 – 0.71)
ACCI score	*0.270*	0.684 (0.58 – 0.79)
ASA score	*0.210*	0.635 (0.51 – 0.76)

indicating discriminatory power for postoperative mortality. A similar result was found for O-POSSUM, ROC curve analysis revealed discriminatory capability for postoperative deaths with an AUC of 0.756 (95% CI: 0.67 to 0.84; p = 0.000).

Evaluation of the Charlson and ACCI score

In our cohort the Charlson score ranged from 0 to a maximum of 4 points. Patients with a Charlson score of 0 points had an observed postoperative mortality of 5.6% (8 patients), score of 1 point: 4.9% (4 patients), score of 2 points: 11.4% (4 patients), score of 3 points: 12.5% (2 patients) and none with a score of 4 points (Table 5). The Age Adjusted Charlson

Table 5. Outcomes of Charlson, ACCI and ASA score

Charlson score	Patients (N)	Observed mortality (%) (N)
0	143	5.6% (8)
1	82	4.9% (4)
2	35	11.4% (4)
3	16	12.5% (2)
4	2	0.0% (0)
ACCI score		
0	20	0.0% (0)
1	55	0.0% (0)
2	64	7.8% (5)
3	71	7.0% (5)
4	39	12.8% (5)
5	15	0.0% (0)
6	12	25.0% (3)
7	2	0.0% (0)
ASA score		
1	36	0.0% (0)
2	177	6.2% (11)
3	60	8.3% (5)
4	5	40.0% (2)

score in the study group ranged from 0 to 7 points and showed similar postoperative mortality rates; with in general increased risk of mortality with higher scores (Table 5). The Hosmer and Lemeshow goodness of fit test, when applied to the Charlson score, indicated a good fit to the observed postoperative deaths ($\chi^2 = 0.833$, 2df, $p = 0.659$), as well as the ACCI score, which showed a similar fit to the observed data ($\chi^2 = 5.174$, 4df, $p = 0.270$; Table 4). The area under the ROC curve for the Charlson score was 0.567 (95% CI: 0.42-0.71; $p = 0.344$) indicating no discriminatory power. Similar results were found regarding the area under the ROC curve for the ACCI score, there was a same poor discriminatory power; 0.684 (95% CI: 0.58-0.79; $p = 0.009$). Since neither of the models showed a good fit with the observed data, they were not divided into risk categories.

Evaluation of the ASA score

There was no postoperative death in the group of patients with an ASA score 1. Patients with an ASA score of 2 had an observed postoperative mortality rate of 6.2% (11 patients) and in the subsequent ASA 3 score, five deceased patients (8.3%) were observed. In the highest ASA score 4, the observed mortality increased to 40.0% (two patients; Table 5). Using the Hosmer and Lemeshow goodness-of-fit test, no significant difference could be found between the observed and expected frequencies in the ASA classification ($\chi^2 = 1.570$ 1df, $p = 0.210$; Table 4). The area under the ROC curve (0.635, 95% CI: 0.51-0.76; $p = 0.055$) did not indicate a discriminatory power. Therefore, the ASA score was not divided into risk categories.

Specification of mortality incidence during the time period

To identify possible differences related to changes in practice over the time, the study time (1991-2007) was divided in three 5-year segments. The 90-day mortality rate was not significantly different compared to the overall mortality of 6.5%: i.e 5.8% from 1991-1996 ($p = 0.854$), 8.8% from 1997-2002 ($p = 0.396$) and 5.7% from 2003-2007 ($p = 0.721$). However, a significant part of the patients who deceased postoperatively had one or more severe comorbidity ($p = 0.018$). Of cardiovascular disease which occurred frequently, TIA/CVA ($p = 0.007$) was observed significantly more during 1991-1996, hypertension ($p = 0.019$) more between 1997-2002 and angina pectoris ($p = 0.000$) more between 2003-2007 (Table 6). Additionally, the predictive power of each model did not differ in these three time periods and both POSSUM models had the strongest predictive power in each time period.

Table 6. Survival and comorbidity rates in patients during three time periods

	Postoperative survivors in periods (%)				Postoperative deceased patients in periods (%)			
	overall	91-96	97-02	03-07	overall	91-96	97-02	03-07
90-day mortality	*260 (93.5)*	81 (94.2)	62 (91.2)	119 (94.4)	*18 (6.5)*	5 (5.8)	6 (8.8)	7 (5.6)
Comorbidity								
Yes/No	114/146	24/57	27/35	63/56	13/5	2/3	4/2	7/0
Diabetes Mellitus	28 (10.8)	5 (6.2)	8 (12.9)	15 (12.6)	3 (16.7)	1 (20.0)	2 (33.3)	0 (0.0)
Hypertension	52 (20.0)	7 (8.6)	8 (12.9)	37 (31.1)	5 (27.8)	0 (0.0)	3 (50.0)	2 (28.6)
COPD	33 (12.7)	4 (4.9)	8 (12.9)	21 (17.6)	1 (5.6)	0 (0.0)	0 (0.0)	1 (14.3)
Angina pectoris	33 (12.7)	11 (13.6)	4 (6.5)	3 (2.5)	3 (16.7)	0 (0.0)	0 (0.0)	3 (42.9)
Congestive heart failure	3 (1.2)	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction								
TIA/CVA	28 (10.8)	10 (12.3)	4 (6.5)	14 (11.8)	3 (16.7)	1 (20.0)	0 (0.0)	2 (28.6)
	14 (5.4)	1 (1.2)	3 (4.8)	10 (8.4)	2 (11.1)	1 (20.0)	0 (0.0)	1 (14.3)

COPD: Chronic Obstructive Pulmonary Disease
TIA/CVA: Transient Ischaemic Attack/ Cerebro Vasculair Accident

DISCUSSION

Risk stratification in high-risk cancer surgery is pivotal in identifying patients who may benefit from specific perioperative management strategies. Although it is difficult to define risk factors associated with adverse outcome in individual patients, evaluation of postoperative mortality and morbidity is not only necessary for adequate preoperative selection of patients but also for a reliable auditing process comparing outcomes across surgeons and hospitals. In the present study from a single tertiary-care referral center, statistical analyses demonstrated the most accurate individual risk probabilities for O-POSSUM. Overall postoperative mortality was well predicted by the P-POSSUM equation with a low rate of underprediction (N = 1). Therefore, in our cohort the P-POSSUM equation is the most powerful predictor when comparing different cohorts.

There seems to be a contradiction between the overestimated value of postoperative mortality by O-POSSUM and its accurate calibration and discriminatory power for an individual patient. However, predictive accuracy refers to the ability of a model to assign the correct probability of death to patients, whereas discriminatory power refers to the ability of a model to attribute the correct outcomes to patients[24].

External validation showed varied results regarding prognostic values for these risk-prediction models [11-13, 21-27]. Two studies, which compared the P-POSSUM and O-POSSUM equation, demonstrated a poor HLG of fit for O-POSSUM, while one suggested good predictive power for P-POSSUM [25,26]. Several studies evaluated the O-POSSUM equation and found a variety of results ranging from moderate to good fit [13,24]. Only a few studies were performed to validated the predictive power of Charlson-, ACCI-, and ASA score after esophagectomy [11,12]. In a recent study, an association has been suggested between a high Charlson score (> 2) and mortality [11], two other studies indicated a relationship between mortality and ASA score [12,21].

These varied results may have several causes. In the first place, these risk-adjusted models could be interpreted in various ways by investigators. For example, the ASA score is defined by an individual anaesthetist at a specific moment and assessments might be influenced by variations in the clinical presentation. Moreover, the ASA score is interobserver dependent and prone to allocation variation.

A second important difference lies in the definition of mortality. The majority of the conducted studies used 30-day mortality as a determinant of surgical outcome, while others used in-hospital mortality. In the present study we used the overall postoperative mortality, defined as in-hospital and 90-day mortality. Most of the applied risk prediction models are developed to calculate mortality risk, without any corrections regarding post-admission death within a reasonable period. In applying the 90-day mortality, we included all operation-related deceased patients. None of these patients deceased on other circumstances rather than on the impact of the surgery. As many patients have a predictable short life span we have to rethink the value of a therapeutic strategy, if much time was spent to recuperate from major surgical stress.

Thirdly, since hospital volume appeared to be an import prognostic value [6], it would be difficult to identify predictive risk factors, particularly in an heterogeneous group. Therefore, we only examined patients who underwent a uniform surgical approach, including a transthoracic esophagectomy with a 2-field lymphadenectomy in a tertiary referral centre with a high hospital and surgeon volume. Although still prematurely, recent literature showed a decrease in severity and frequency of morbidity in patients who underwent a laparoscopic approach, but evidence for a reduced mortality has not been established yet [27,28]. None of the patients in this study had a laparoscopic approach and further research is necessary to examine the applicability of these risk prediction models in such a cohort.

A drawback of this study lies in the time span of 16 years. A number of factors affecting survival may have evolved over this period of time such as better patient selection or newer technology, including neoadjuvant chemoradiation and surgical approaches. To counteract the possibility of interfering factors over this period, we divided the time span in three almost equal segments. Mortality rates didn't differ significantly over this period and statistical analysis indicated the most predictive power for both POSSUM models in each segment. The influence of neoadjuvant chemoradiation in this study was low as there was no mortality in this rather small group of patients (n = 10).

Recently, new risk-adjusted models were developed, including the Rotterdam-, Philadelphia- and Munich score to compare cohorts, but they do not provide individual risk stratification as was clearly concluded by Zingg et al [29].

So far a reliable individual risk analysis stratification to guide surgeons and oncologists in the decision-making is missing and it should be done in the context of an overall clinical judgment. With a more appropriate risk-prediction model, we might be able to identify patients with high estimated morbidity and mortality. A careful selection based on such models may be helpful to perform adequate preoperative interventions and reducing the risk of postoperative complications.

Current centralization of this high-risk surgery has led to a relatively low postoperative morbidity and better outcome has been observed in high-volume centers for moderate- to high-risk patients. [30] Predicting the mortality risk in an individual patient is difficult. The number of events is too few to justify clinical application of any scoring system without further validation with prospective data in the setting of a clinical trial. To counteract the impossibility of the current models in selecting the individual at-risk patient, we subdivided the most accurate model into a low, intermediate and high-risk category. The benefit of this subdivision for a model is no longer the identification of a rare event, but to identify a group of patients with an increased mortality risk. Thereby, it would be a benefit for the informed consent and usefulness of a model; since it is immediately obvious to which risk group a patient belongs. To justify this distribution in clinical practice, more research is necessary to validate this quantification.

CONCLUSION

Each risk-adjusted model demonstrated a moderate relationship between postoperative mortality and an increased risk score. We recommend the O-POSSUM for individual risk stratification as it assessed the condition of the patient and the risk of surgery most accurately in this study. In clinical practice we suggest dividing the O-POSSUM score into a low, intermediate and high-risk category, but before general application more research is needed to validate our findings.

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Increased risk of thromboembolism in esophageal cancer patients treated with neoadjuvant chemoradiotherapy

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy (CRT) in esophageal cancer (EC) patients may increase the formation of thromboembolic events (TEE's). We analyzed the incidence and impact of TEE's in EC patients treated with platinum-based CRT.

Patient and methods: A total of 336 patients with EC underwent an esophagectomy of which 110 patients received neoadjuvant CRT (41.4Gy with concurrent Carboplatin/Paclitaxel). Patients were matched based on pre- and perioperative characteristics.

Results: Preoperatively, 9 (8.2%) patients with neoadjuvant CRT ($p = 0.004$) were diagnosed with TEE's. Despite delay until surgery ($p = 0.021$), the postoperative course did not differ. In multivariate analysis, a history of DVT ($p = 0.005$) and neoadjuvant CRT ($p = 0.004$) were identified as risk factors. Postoperatively, there was no differences in TEE's ($p = 0.560$) observed. In multivariate analysis, a history of pulmonary embolism ($p = 0.012$) was identified as risk factor for postoperative TEE's.

Conclusion: Preoperatively, EC patients treated with neoadjuvant CRT have an increased risk to develop a TEE, especially those with a previous history of TEE. After surgery no increased incidence was observed. We recommend secondary prophylaxis during neoadjuvant treatment in this high-risk group.

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection is a widely accepted curative intended treatment in patients with esophageal cancer (EC). Depending on oncological and conditional criteria, patients receive in our center radiotherapy (41.4Gy/5wks) and concurrent chemotherapy (Carboplatin and Paclitaxel) according to the CROSS regimen. This platinum-based neoadjuvant CRT improves loco-regional control and overall survival with 13% at 5 years(1).

As distinct from this benefit, neoadjuvant CRT may subsequently be accompanied by an increased risk for adverse pre- and postoperative complications(2). It is known that cancer patients, especially those with gastro-esophageal cancer, generally have a high risk of venous thrombosis(3, 4). Moreover, the use of chemoradiotherapy seems to be associated with a further enhanced risk of developing thromboembolic events (TEE's), including deep vein thrombosis (DVT) and pulmonary embolism (PE)(5-9).

In the mid-nineteenth century Virchow and Trousseau described the pathophysiology of TEE's in cancer patients. However, there still exist significant gaps in the understanding of cancer-associated TEE's in patients treated with chemotherapy alone or combined with radiotherapy. Reported incidences of TEE's during chemotherapy for EC are approximately 10 to 12%, and partly depending on the type of chemotherapy(9). The risk of TEE's in currently used neoadjuvant CROSS regimen is, according to our knowledge, not previously described. The hypothesis in the present study was that neoadjuvant platinum-based CRT in esophageal cancer patients is accompanied with an increased incidence of TEE's.

PATIENTS AND METHODS

Patient's characteristics

In this study, we included all 336 patients who underwent a transthoracic esophagectomy with curative intent between January 2000 and December 2012. Of these patients 110 (32.7%) received neoadjuvant CRT followed by surgery between January 2006 and December 2012. Patients with unforeseen progression of their disease were excluded (N = 5). All data was collected prospectively, including: demographic and tumor characteristics, comorbidity, therapeutic information, details about neoadjuvant treatment, medication, pre- and postoperative complications, and survival data.

To reduce bias in selection criteria and interfering factors in developing TEE's, we created statistically comparable groups by propensity matching. The propensity score is used to balance covariates allowing two study subjects with the same propensity score to be appreciably similar in observed dimensions (implemented in our SPSS package(10)). Patients treated with neoadjuvant CRT (N = 110) were matched with 95 patients who were treated between 2000 and 2012 with surgery alone. Patients were matched for: sex, medical history of deep venous thrombosis (DVT), pulmonary embolism, myocardial infarction, and TIA/CVA, ASA classification, and preoperative cTstage.

Neoadjuvant chemoradiotherapy

Patients who were eligible for neoadjuvant CRT received Carboplatin, which was administered weekly with a targeted area under the curve (AUC) of 2 mg per milliliter per minute and Paclitaxel of 50 mg/m2 for 5 weeks. Concurrent radiotherapy, which consisted of 41·4 Gy in 23 fractions of 1·8 Gy, was administered five times per week. Radiotherapy target volumes were delineated on a planning computed tomography (CT) scan by an experienced radiation oncologist. Oncologic criteria consisted of a clinical tumor stage of T1N1-3 or T2-T4aN0-3 without distant metastases (M0). Conditional requirements were based on the judgment of the surgeon and both the medical and radiation oncologist and were comparable to the eligibility criteria of the national CROSS study(1).

Preoperative evaluation and comorbidity

All patients were staged with an endoscopic ultrasonography (EUS) including fine needle aspiration (FNA) and 16-64 slice spiral multidetector computed tomography (MDCT) with intravenous and oral contrast of the neck, chest, and abdomen. In locally advanced tumors (T3-4a or N1-3), an 18F-fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET) was performed. For the final analysis, the available reports of every EC patient were reviewed and discussed in a multidisciplinary tumor specific board to assess appropriate management. Patients treated with surgery alone underwent an esophageal resection within 4-8 weeks after staging. In patients treated with neoadjuvant CRT, a restaging MDCT with intravenous contrast of the neck, chest, and abdomen was performed to exclude progressive disease in assessing resectability.
Comorbidity was classified according to the American Society of Anesthesiology (ASA) score varying from ASA 1 (very good condition) to ASA 5 (moribund patient). The ASA score is a readily available and widely accepted method to stratify surgical patients according to their pre-operative risk.

Surgery

All patients underwent, usually within 4-8 weeks after (re)staging, a transthoracic esophagectomy with two-field lymphadenectomy by two experienced surgeons. Distal tumors and those around the gastro-esophageal junction were approached through a left thoraco-laparotomy and intrathoracic anastomoses by gastric-tube reconstruction. More cranial located esophageal tumors were approached through a right thoraco-laparotomy with cervical anastomoses.

TEE prevention

Patients using preoperative anticoagulation and those diagnosed with a TEE during neoadjuvant CRT, were instructed to use a therapeutic dosage (11400 units a day) of low molecular weight heparin (LMWH), which was adjusted to a prophylactic dose (2850 units a day) 5 days before surgery. This was administered by specialized home care nurses. In all patients, LMWH was started perioperatively and continued until discharge. Dosage was dependent on patient's weight and risk-factors and varied between 2850 and 11400 units a day. In addition, all patients received compression stockings for the first 24 hours after surgery.

Definition of outcome

The primary outcome was based on the occurrence of TEE's pre- and/or postoperative. Venous, arterial, symptomatic, and idiopathic TEE's were included. In patients treated with neoadjuvant CRT, a staging multidetector CT (MDCT) with intravenous and oral contrast was performed < 4 weeks before CRT. In all patients, regardless of treatment, a MDCT with intravenous and oral contrast was performed < 4-8 weeks before surgery. If pulmonary embolism was diagnosed, an upper and lower ultrasonography was performed. Patients presented with clinical symptoms of TEE underwent an additional triphasic CT-angiography to confirm the diagnosis. Clinical suspected TEE's of the extremities were confirmed by duplex ultrasonography. A preoperative TEE took place between diagnosis of esophageal cancer and surgery. Postoperative TEE's occurred during hospital admission and examination consisted of CT-angiography if central embolisms were suspected and duplex untrasonography to confirm TEE's of the extremities. Thromboembolic events were scored according to the National Cancer Institute common toxicity criteria for adverse events (CTCAE version 4.03.13) (Table 1). Short-term mortality included in hospital mortality and/or mortality within the first 90 days after surgery.

Table 1. Grading of thromboembolic events according to the Common Terminology Criteria for Adverse Events (CTCAE) definition:

Grade	Definition
1	Venous thrombosis (e.g. superficial thrombosis)
2	Venous thrombosis (e.g. uncomplicated deep vein thrombosis), medical intervention indicated
3	Thrombosis (e.g. uncomplicated pulmonary embolism, non-embolic cardiac mural thrombus), medical intervention indicated
4	Life-threatening (e.g. pulmonary embolism, cerebrovascular event, arterial insufficiency) hemodynamic or neurologic instability, urgent intervention indicated
5	Death

Statistical analysis

Data is reflected as frequencies, means and/or median with percentages. Categorical variables were analyzed with the χ^2 test, and continuous variables were analyzed with a Student t test (normal distribution) or Mann Whitney U-test (skewed distribution). Univariate regression analysis was used to determine risk factors for the development of TEE's. Multivariate logistic regression was applied to correct for cofounders. A p-value < 0.05 was considered to be significant. Statistical analyses were conducted by the statistical software from SPSS 20.0 (SPSS Inc., Chicago IL, USA).

RESULTS

Median age in this cohort was 65.8 years and the majority was diagnosed with adenocarcinoma 83.3% (N = 280). Hypertension (30.4%) and diabetes mellitus (12.8%) were the most frequently reported comorbidities. A considerable number of patients had a thromboembolic event in medical history, including pulmonary embolism in 2.4% (N = 8) and myocardial infarction in 12.2% (N = 41) (Table 2).

The majority (80.1%) of the patients underwent the full neoadjuvant treatment regimen. For various reasons and complications during neoadjuvant CRT, 20 patients (18.2%) received four out of five cycles of chemotherapy and three patients (2.7%) received three cycles or less. Most frequently reported complications during neoadjuvant CRT consisted of hematological toxicity (N = 11; 10.0%) (Table 3).

Matching

No differences were observed in comorbidity, histology, localization, and side of thoracotomy between patients with surgery alone and patients treated with neoadjuvant CRT followed by surgery (Table 2). However, patients treated with neoadjuvant CRT had comprehensible a lower ASA classification (p = 0.003). Besides, a significant difference in preoperative T stage (p = 0.032) was observed. These variables might influence the development of TEE's. After matching, statistically comparable groups were created, with 95 patients in the surgery alone group and 110 patients in the neoadjuvant CRT followed by surgery group (Table 2).

Thromboembolic events

In the whole cohort (N = 336), 24 patients (7.1%) were diagnosed with a TEE at some stage during treatment, 10 (3.0%) events developed in the preoperative phase and 14 (4.2%) arose postoperatively. Patients who were treated with neoadjuvant CRT were diagnosed with 12 TEE's (10.9%) with a relative risk of 2.645 (95% confidence interval (CI); 1.105-6.329, p = 0.029).

Table 2. Patients and tumor characteristics; surgery alone vs. neoadjuvant CRT followed by surgery.

Characteristic	Surgery alone (%)		Neoadjuvant CRT followed by surgery (N = 110) (%)	p-value unmatched	p-value matched
	Unmatched (N = 226)	Matched (N = 95)			
Gender (M/F)	180/45	71/24	83/27	0.331	0.906
Age (years)	65.5	64.2	63.0	0.228	0.557
Smoking	70 (31.0)	34 (35,8)	48 (43.6)	0.258	0.375
Comorbidity					
Angina pectoris	20 (8.8)	5 (5.3)	10 (9.1)	0.942	0.294
Myocardial infarction	30 (13.3)	10 (10.5)	11 (10.0)	0.390	0.901
Heart failure	6 (2.7)	1 (1.1)	2 (1.8)	0.637	0.649
Hypertension	64 (28.3)	25 (26.3)	38 (34.5)	0.244	0.203
Diabetes mellitus	27 (11.9)	9 (9.5)	16 (14.5)	0.503	0.268
TIA/CVA	21 (9.3)	4 (4.2)	7 (6.4)	0.362	0.495
Pulmonary embolism	7 (3.1)	0 (0.0)	1 (0.9)	0.217	0.352
DVT	7 (3.1)	0 (0.0)	2 (1.8)	0.496	0.187
ASA classification					
ASA I	11 (4.9)	10 (10.5)	13 (11.8)		
ASA II	130 (57.5)	71 (74.7)	66 (60.0)		
ASA III	67 (29.6)	14 (14.7)	16 (14.5)		
ASA IV	5 (2.2)	0 (0.0)	0 (0.0)		
Missing	13 (5.8)	0 (0.0)	15 (13.6)	**0.003**	0.702
Histology					
Adenocarcinoma	190 (84.1)	75 (78.9)	90 (81.8)		
SCC	36 (15.9)	20 (21.1)	20 (18.2)	0.728	0.512
Clinical T stage					
T1	29 (12.8)	3 (3.2)	0 (0.0)		
T2	32 (14.2)	12 (12.6)	19 (17.3)		
T3	158 (69.9)	75 (78.9)	86 (78.2)		
T4	7 (3.1)	5 (5.3)	5 (4.5)	**0.032**	0.235
Localization					
Mid esophagus	25 (11.2)	14 (14.7)	14 (12.7)		
Distal esophagus	160 (71.4)	62 (65.3)	85 (77.3)		
GEJ	39 (17.4)	19 (20.0)	11 (10.0)	0.201	0.097
Thoracotomy					
Left sided	100 (44.2)	33 (34.7)	41 (37.3)		
Right sided	126 (55.8)	62 (65.3)	69 (62.7)	0.224	0.706

TIA/CVA: transient ischemic attack/ cerebrovascular accident, DVT: deep venous thrombosis, ASA: American Society of Anesthesiologists, SCC: Squamous cell carcinoma, GEJ: gastro-esophageal junction

In the matched cohort (N = 205), 16 patients (7.8%) were diagnosed with a TEE of which 9 (4.4%) occurred preoperatively and 7 (3.4%) postoperatively (Table 3). In this cohort, the relative risk to develop a TEE for patients treated with neoadjuvant CRT was 3.755 (95% CI: 1.027-13.734 p = 0.046).

Table 3. Complications during neoadjuvant CRT.

Complications	Neoadjuvant CRT followed by surgery (N = 110) (%)	Grade *			
		1	2	3	4
Thrombocytopenia	5 (4.5)	-	4	1	-
Leukopenia	7 (6.4)	1	3	3	-
Thromboembolic event	9 (8.2)	-	1	7	1
Fever	4 (3.6)	2	2	-	-
Fatigue	2 (1.8)	-	2	-	-
Dyspnea	1 (0.9)	-	1	-	-
Neurotoxic effects	3 (2.7)	2	1	-	-
Nausea	2 (1.8)	-	1	1	-
Anorexia	4 (3.6)	-	3	1	-
Aspiration pneumonia	1 (0.9)	-	1	-	-
Angina pectoris	2 (1.8)	-	2	-	-
None	80 (72.7)	-	-	-	-

* Grading according to CTCAE v3.0

Preoperative TEE

During the preoperative period in the unmatched cohort, 10 patients were diagnosed with a TEE of which 9 patients were treated with neoadjuvant CRT (p = 0.000). In the matched cohort all preoperative TEE's (N = 9, 8.2%) were exclusively observed in the group treated with neoadjuvant CRT (p = 0.004). Thromboembolic events consisted of DVT (N = 2), pulmonary embolism (N = 7) and portal vein thrombosis (PVT; N = 1) (Table 4). One patient was diagnosed with a DVT and pulmonary embolism at the same time.

The majority of the preoperative TEE's were asymptomatic (pulmonary embolism: N = 6 and PVT: N = 1, CTCAE 3; definition Table 1). None of these TEE's were diagnosed on the first staging CT-scan, but were diagnosed on the second i.e restaging CT-scan after neoadjuvant CRT. One patient experienced acute symptoms of a pulmonary embolism (CTCAE 4).

Patients who were diagnosed with a preoperative TEE had a median of 60 days between end of neoadjuvant CRT and surgical resection compared to 48 days for patients without the presence of a TEE (minimum 41 days, maximum 236 days) (p = 0.021). This delay had no influence on the surgical decision to perform a radical resection. None of these patients were excluded from surgery. Patients who were using anti-coagulation (i.a. heparin, acenocoumarol or thrombocyte aggregation inhibitors) did not have a reduced risk on the formation of TEE's (p = 0.758). Besides, the presence of TEE treated preoperatively had no influence on postoperative complications, hospital stay or short-term mortality.

A multivariate analysis was performed to correct for cofounding factors for developing preoperative TEE's. History of DVT (p = 0.005; odds ratio (OR): 37.429; 95% CI: 3.025-463.117)

Table 4. Thromboembolic events during EC treatment.

Thromboembolic events	Surgery alone		Neoadjuvant CRT followed by surgery (N = 110)	p-value unmatched	p-value matched
	Unmatched (N = 226)	Matched (N = 95)			
Preoperative					
DVT	1	0	2	0.208	0.187
Pulmonary embolism	0	0	7	**0.000**	**0.012**
PVT	0	0	1	0.487	0.708
Patients with a TEE	1	0	9	**0.000**	**0.004**
Postoperative					
DVT	1	0	1	0.602	0.352
CVA	2	1	0	0.322	0.281
Myocardial infarction	1	0	0	0.845	-
Pulmonary embolism	7	3	2	0.496	0.535
Patients with a TEE	11	4	3	0.357	0.560

DVT: deep venous thrombosis, PVT: portal vein thrombosis, CVA: cerebrovascular accident

and treatment with neoadjuvant CRT (p = 0.004; OR: 34.519; 95% CI: 3.086-386.101) were identified as possible risk factors (matched cohort).

Postoperative TEE

A thromboembolic complication in the postoperative course was a relatively rare event (N = 14; 4.2%). In the unmatched cohort 11 patients (4.8%) with surgery alone developed a TEE compared to 3 patients (2.7%) treated with neoadjuvant CRT (p = 0.357). These events varied between DVT (surgery alone: N = 1 and neoadjuvant CRT followed by surgery: N = 1), CVA (surgery alone: N = 2), myocardial infarction (surgery alone: N = 1) and pulmonary embolism (surgery alone: N = 7 and neoadjuvant CRT followed by surgery: N = 2) without significant differences between groups. The occurrence of a TEE in the matched cohort was not significantly different between both groups (N = 4 vs. N = 3; p = 0.560) (Table 4).

Two patients deceased within 90 days and/or in-hospital due to the consequences of a TEE (myocardial infarction and pulmonary embolism, CTCAE 5). These events were exclusively observed in patients who underwent surgery alone. Hospital- (p = 0.936) and ICU stay (p = 0.375) did not differ between patients with and without TEE's (matched cohort). Compared to preoperative risk factors, postoperative risk factors analyses for the development of TEE's were extended with ICU/hospital stay and side of thoracotomy. However, the only possible risk factor that exceeded the threshold in univariate analysis was a history of pulmonary embolism (p = 0.012; OR: 8.778; CI 95%: 1.602-48.095).

DISCUSSION

Cancer patients generally present with a higher risk of thromboembolic events (TEE's) and with the introduction of neoadjuvant chemoradiotherapy the incidence of TEE's seems to increase further (6, 9, 11). In this study, we observed a higher risk of preoperative thromboembolic events in EC patients treated with platinum-based neoadjuvant CRT. Despite a possible long-lasting effect of chemoradiotherapy, we could not demonstrate a different postoperative incidence. Although the majority of the preoperative diagnosed TEE's were idiopathic, one patient experienced acute and life-threatening symptoms of a pulmonary embolism during neoadjuvant CRT (CTCAE 4).

The pathophysiological mechanism is not fully understood, but chemotherapy appears to play a major role in pro-inflammatory and pro-coagulant response due to endothelial disruption. Inflammatory response is initiated by cytokines, in particular TNF-a and IL-1, which decrease the concentration of important anti-coagulant proteins, including antithrombin and protein C. Pro-coagulant response is initiated by an increased tissue factor expression(6, 12). Moreover, the activated pro-coagulant response is sustained for up to 6 months after induction of chemoradiotherapy, which implies an increased postoperative risk for TEE's over a longer period of time(7).

Most scientific research concerning TEE's in cancer patients is related on patients with advanced malignancies undergoing palliative treatment. Only a few studies focused on the incidence of TEE's in patients who were treated with curative intent in a multimodality approach(5, 7, 8). In a study of Verhage et al. patients with pre- and postoperative chemotherapy showed a significant increased incidence of preoperative TEE's(5). In addition, Byrne et al. gave the pathophysiological explanation for an increased risk of TEE's in a multimodal treatment(7). In gastro-esophageal cancer patients treated according to the CROSS regimen, the risk for TEE's is not previously described(1). Additional risk factors for cancer-associated TEE's are well documented in the literature and are generally based on cancer treatment –and patient related factors(4). In accordance to our results, a past history of thrombotic events is a risk factor for developing TEE's.

In the current study, we applied perioperatively thromboprophylaxis with compression stockings and low molecular weight heparin (LMWH), which was continued until discharge. Nevertheless, 14 patients were diagnosed with postoperative TEE's of whom two were fatal (surgery alone group). Generally, patients did not receive primary or secondary thromboprophylaxis in the preoperative period. The value and safety of prophylaxis during chemoradiotherapy is questionable, as it may contribute to an increased risk of bleeding in combination with chemotherapeutic induced thrombocytopenia (13). The incidence of thrombocytopenia in this study is probably underestimated due to the retrospective nature of this research. In a Cochrane review the authors stated that the number needed-to-treat to prevent a symptomatic TEE was 60 without any clear benefit in survival, but with an increased risk of complications(13). Preoperative TEE's in the present study were not only associated with chemoradiation, but also with a history of DVT. Hence, current guidelines recommend secondary thromboprophylaxis in cancer patients with a history of TEE's(14). Notwithstanding the lack of an appropriate study design, but based on the results of present study and previous published guidelines, we recommend the use of secondary thromboprophylaxis during neoadjuvant CRT in EC patients with a history of TEE's. In our opinion, it is preferable to start thromboprophylaxis with LMWH under adequate hematological control(15).

The majority of preoperatively diagnosed TEE's in the present study were asymptomatic. None of these TEE's in patients treated with neoadjuvant CRT were diagnosed at the first staging CT-scan, but during the second i.e restaging CT-scan 4-8 weeks prior to surgery. The staging CT-scan in patients within the surgery alone group also was performed < 4-8 weeks before surgery. We therefore do not expect an underestimated incidence of preoperatively diagnosed TEE's in patients without neoadjuvant CRT. In current study, patients without clinical suspicion of TEE did not undergo a triphasic CT-angiography. However, the diagnostic accuracy of currently used multislice MDCT with intravenous contrast seems to be of sufficient quality in diagnosing pulmonary embolism, especially when combined with an upper and lower ultrasonography(16-18). Therefore, we consider the impact of neoadjuvant CRT on the development of TEE's plausible by this study and available literature(5, 7-9, 13). Nevertheless, with one symptomatic pulmonary embolism, the impact of TEE's seems relatively moderate. And in spite of a significant delay until surgery, there seemed to be no influence on surgical resection and postoperative course(8).

In conclusion, patients treated with neoadjuvant CRT for esophageal cancer have an increased risk to develop TEE's for surgical resection, especially with TEE's in medical history. Postoperatively we observed no difference in incidence. We therefore, make a plea for secondary prophylaxis in this high-risk group with LMWH.

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Impact of neoadjuvant chemoradiotherapy on postoperative course after curative intended transthoracic esophagectomy in esophageal cancer patients

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy (CRT) improves loco-regional control and overall survival in esophageal cancer patients. Although adverse events are relatively low during neoadjuvant CRT, severe postoperative side-effects may occur leading to morbidity and even mortality. We investigated the impact of a more frequently used neoadjuvant CRT regimen of 41.4Gy/5wks radiotherapy with concurrent Carboplatin and Paclitaxel (CROSS schedule) on the postoperative course.

Methods: Between 2006 and 2012, a total of 96 esophageal cancer patients (staged cT1N+/T2-4a/N0-3 and M0) were treated according to the above neoadjuvant scheme. To reduce bias in this single center study, we performed a propensity score matched analysis with patients who underwent surgery alone (n = 230), from a prospectively maintained database (n = 326).

Results: Baseline characteristics between both groups were equally distributed in the matched cohort. In the neoadjuvant treated group significantly more patients were diagnosed with pneumonia (27.1% vs. 51.0%; p = 0.001), pleural effusion (12.5% vs. 24.0%; p = 0.040), and arrhythmias (20.4% vs. 34.4%; p = 0.008). Besides, in the multivariate analysis neoadjuvant CRT was significantly associated with an increased risk of pneumonia (p = 0.001, odds ratio (OR) 2.896), pleural effusion (p = 0.041, OR 2.268), and arrhythmia (p = 0.023, OR 2.215). Despite these outcomes, no differences were detected in ICU - or hospital stay. Short-term mortality did not differ between both groups.

Conclusions: In this study, we observed an increase of cardiopulmonary complications in the neoadjuvant CRT group, which has no effect on hospital or ICU stay and mortality. Further research is warranted on limitation of chemoradiotherapy-induced cardiopulmonary toxicity.

INTRODUCTION

Survival in esophageal cancer patients after curative intended surgery alone remains poor with an average 5-year disease free survival between 15–25% [1]. To improve loco-regional control and overall survival, a multimodality approach with neoadjuvant chemo-radiotherapy (CRT) has become standard of care in most centers. Significant survival benefit of 13% at 5 years after neoadjuvant CRT has been demonstrated in a multicenter randomized clinical trial, the CROSS study [2]. Based on their results and the outcome in the literature over the last decades, the authors make a plea for standardization of preoperative CRT[2-15].

Transthoracic esophagectomy is generally considered to be a high-risk surgical procedure with complication rates ranging between 40-60% [16]. With an even more onerous treatment policy, concerns have been raised about the impact of neoadjuvant CRT on the postoperative course. Chemotherapy prior to a radical esophagectomy may subsequently be accompanied by the risk of acute and late toxicity. Adding thoracic radiotherapy to a combined chemotherapy regimen will further increase cardiopulmonary toxicity [17, 18]. It might induce acute inflammation resulting in pneumonia, pleural effusion and finally lung fibrosis and is associated with a significant cardiac toxicity [19].

Nevertheless, promising results for long term survival have led to several randomized controlled trials (RCT's) and subsequent meta-analyses [2, 9-15, 20]. Some studies described an increased postoperative morbidity and even mortality, which was not the case in the CROSS trial. However, postoperative morbidity in that study was described without further specification in postoperative complications.

With aging of the population and increased incidence of esophageal cancer in western countries the use of neoadjuvant CRT will further increase. Especially in elderly patients the prevalence of comorbidity is relatively high and we should consider whether long-term survival benefits outweigh the potential disadvantages of higher complication rates [4]. In addition, comorbidities contribute to complexity and restricting patients from CRT in the pretreatment assessment remains difficult. In this study we aimed to investigate the influence of neoadjuvant CRT on the short-term postoperative course after a curative intended transthoracic esophagectomy.

PATIENTS AND METHODS

Patient characteristics

From a prospectively maintained database we included all 326 esophageal cancer patients, who underwent an extended transthoracic esophagectomy with curative intent between January 2000 and June 2012. From this group we collected the following data: demographic characteristics, comorbidity, neoadjuvant treatment, tumor characteristics, therapeutic information, complications, and survival data. Of these 326 patient, 96 patients were treated with the CROSS regimen. To reduce bias in selection criteria and interfering factors in postoperative complications, we created statistically comparable groups by propensity matching. The propensity score is used to balance covariates allowing two study subjects with the same propensity score to be appreciably similar in observed

Table 1. Patient characteristics

Variable	Surgery alone (%)		Neoadjuvant CRT followed by surgery N = 96 (%)	p-value unmatched	p-value matched
	unmatched N = 230	matched N = 96			
Median age (yrs)	65.0	63.1	62.7	0.427	0.432
Sex (M/F)	180/50	72/24	71/25	0.400	0.869
Smoker	30.6	34.7	42.7	0.205	0.258
Histology					
Adenocarcinoma	191 (83.0)	79 (82.3)	77 (80.2)	0.608	0.527
Squamous CC	37 (16.1)	16 (16.7)	19 (19.8)		
Other	2 (0.8)	1 (1.0)	0 (0.0)		
Localization					
Mid	25 (10.9)	10 (10.4)	13 (13.5)		
Distal	162 (70.4)	66 (68.8)	73 (76.0)		
GEJ	43 (18.7)	20 (20.8)	10 (10.4)	0.140	0.123
cT stage					
T1/T2	61 (26.5)	27 (28.1)	23 (24.0)		
T3/T4	169 (73.5)	69 (71.9)	73 (76.0)	0.844	0.492
Comorbidity					
Angina pectoris	18 (7.8)	10 (10.4)	6 (6.3)	0.619	0.296
Myocardial infarct	29 (12.6)	11 (11.5)	8 (8.3)	0.267	0.468
Heart failure	5 (2.2)	2 (2.1)	2 (2.1)	0.959	1.000
Hypertension	66 (28.7)	32 (33.3)	31 (32.3)	0.517	0.878
COPD	33 (14.3)	6 (6.3)	7 (7.3)	0.077	0.774
Diabetes mellitus	27 (11.7)	9 (9.4)	13 (13.5)	0.651	0.365
TIA/CVA	20 (8.7)	3 (3.1)	7 (7.3)	0.675	0.194
ASA classification					
ASA I	11 (5.1)	10 (11.2)	11 (13.6)		
ASA II	136 (62.7)	67 (75.3)	57 (70.4)		
ASA III	65 (30.0)	11 (12.4)	13 (16.0)		
ASA IV	5 (2.3)	1 (1.1)	0 (0.0)	**0.006**	0.649
Thoracotomy					
Right sided	129 (56.1)	56 (58.9)	59 (61.5)		
Left sided	101 (43.9)	39 (41.1)	37 (38.5)	0.285	0.767

dimensions (implemented in our SPSS package [21]). The 96 patients in the neoadjuvant CRT group were matched with 96 patients from the total 230 patients treated with surgery alone. Patients were matched for: age, sex, tumor characteristics, comorbidity (individually scored: diabetes mellitus, hypertension, angina pectoris, heart failure, myocardial infarction, COPD, TIA/CVA), ASA score and side of thoracotomy (Table 1).

Neoadjuvant chemoradiotherapy

Both squamous cell carcinoma and adenocarcinoma of the esophagus were considered suitable for neoadjuvant CRT. Oncologic criteria consisted of a clinical tumor stage of T1N1-3 or T2-T4aN0-3 without distant metastases (M0). During 2006-2008, a part of our cohort participated in the national CROSS study [2]. After 2008 neoadjuvant CRT was administered based on the judgment of the oncologist, on inclusion criteria similar to that used in the CROSS study. Carboplatin was administered weekly to achieve an area under the curve (AUC) of 2 mg per milliliter per minute and paclitaxel of 50 mg/m2 for 5 weeks, with concurrent radiotherapy, which consisted of 41·4 Gy in daily fractions of 1·8 Gy (in 3 patients 45·0 Gy in 25 fractions), five times per week. Radiotherapy target volumes were delineated on a planning CT-scan by an experienced radiation oncologist using all diagnostic information.

Surgery

All patients with cardiopulmonary history were seen by the cardio/pulmonologist for perioperative recommendations. After a restaging CT, 4 weeks after the end of CRT, patients were planned for a surgical resection, usually within 4-8 weeks after neoadjuvant treatment. All patients underwent a transthoracic esophagectomy with two-field lymphadenectomy by two experienced surgeons. Tumors around the gastroesophageal junction were approached through a left thoraco-laparotomy while more cranial located esophageal tumors were approached through a right-sided procedure.

Definitions of outcome

Short-term mortality was defined as “surgical mortality” which included in hospital mortality and/or mortality within the first 90 days after operation. To simplify comparison with previous studies, 30-day mortality was also displayed. Complications during hospital admission were divided into pulmonary, cardiac, and other complications as can be seen in Table 2. Complications were scored on the same criteria as described previously [22], except for pneumonia, which was supplemented with the use of antibiotic treatment on clinical indications.

Comorbidity was classified according to the American Society of Anesthesiology (ASA) score varying from ASA 1 (very good condition) to ASA 5 (moribund patient) [23].

Table 2. Matched data; complications and post-operative course after esophagectomy

Variable	Surgery alone N = 96 (%)	Neoadjuvant CRT followed by surgery N = 96 (%)	p-value
Surgical mortality*	7 (7.3)	7 (7.3)	1.000
30-day mortality	6 (6.3)	3 (3.1)	0.306
Overall complications	60 (62.5)	70 (72.9)	0.123
Pulmonary complications			
Respiratory failure	26 (27.1)	22 (22.9)	0.505
Pneumonia	26 (27.1)	49 (51.0)	**0.001**
ARDS	5 (5.2)	2 (2.1)	0.248
Atelectasis	10 (10.4)	9 (9.4)	0.809
Pleural effusion	12 (12.5)	23 (24.0)	**0.040**
Pulmonary embolism	3 (3.1)	2 (2.1)	0.650
Re-intubation	25 (26.0)	18 (18.8)	0.226
Cardiac complication			
Arrhythmias	20 (20.8)	33 (34.4)	**0.036**
Myocardial infarct	2 (2.1)	0 (0.0)	0.155
Other complications			
SIRS	5 (5.2)	4 (4.2)	0.733
Sepsis	9 (9.4)	7 (7.3)	0.602
Anastomotic leakage	13 (13.5)	11 (11.5)	0.663
Chylothorax	3 (3.1)	7 (7.3)	0.194
Wound infections	9 (9.4)	8 (8.3)	0.799
Wound dehiscence	4 (4.2)	2 (2.1)	0.407
Renal failure	4 (4.2)	4 (4.2)	1.000
Liver failure	0 (0.0)	1 (1.0)	0.316
Ileus	2 (2.1)	4 (4.2)	0.407
Postoperative course			
Reoperation	6 (6.3)	8 (8.3)	0.579
OR-time	7.8 hours	9.0 hours	0.158
ICU-stay	3.5 days	3.0 days	0.954
Hospital stay	16.0 days	16.0 days	0.986

* surg. mortality i.e in hospital and/or 90-day mortality

Statistical analysis

Data was reflected as frequencies, means and/or medians with percentages. Categorical variables were analyzed with the χ^2 test, and continuous variables were analyzed with a Student *t* test (normal distribution) or Mann Whitney *U*-test (skewed distribution). To determine the effect of neoadjuvant CRT on postoperative complications, we performed a multivariate analysis for complications with a p-value < 0.1 in the univariate analyses. A p-value < 0.05 was considered to be significant. All statistical analyses were conducted by the statistical software from SPSS 20.0 (SPSS Inc., Chicago IL, USA).

RESULTS

Differences in demographic characteristics between patients who were treated with surgery alone (group 1, N = 230) and those treated with neoadjuvant CRT combined with surgery (group 2, N = 96), were only observed in ASA classification (p = 0.006) (Table 1). After matching, 96 patients were included in group 1 and 96 in group 2 with an equal distribution of demographic characteristics (Table 1). The majority (95.8%) of this cohort received at least 4 out of 5 cycles of the neoadjuvant CRT scheme.

Mortality and morbidity

Short-term mortality was not significantly different between both groups. In the unmatched cohort we observed a 30-day mortality of 4.3% (n = 14), which was equally distributed between both groups. Surgical mortality in the unmatched cohort, including in-hospital and 90-day mortality, was 7.4% (N = 17) for group 1 and 7.3% (N = 7) for group 2 (p = 0.975). In the matched cohort, surgical mortality was 7.3% (N = 7) for both groups (p = 1.000). Overall morbidity rates in the matched cohort between group 1 (62.5%) and 2 (72.9%) were not significantly different (p = 0.123) (Table 2).

Pulmonary complications in the matched cohort

Overall pulmonary complications were observed more frequently, but not significantly different in patients treated with neoadjuvant CRT (46.9% vs. 59.4%; p = 0.083). Pneumonia was the most commonly reported complication, and occurred significantly more in patients treated with neoadjuvant CRT (27.1% vs. 51.0%; p = 0.001). The number of days between the end of neoadjuvant CRT and surgery had no influence on the occurrence of pneumonia (52 days vs. 53 days; p = 0.137). In addition to pneumonia, also pleural effusion was more frequently observed in patients treated with neoadjuvant CRT (12.5% vs. 24.0%; p = 0.040). The number of days between the end of neoadjuvant CRT and surgery was not significantly different (56 days vs. 52 days; p = 0.958). In contrast to pneumonia, pleural effusion was not significantly different (p = 0.075) in the unmatched cohort. Other pulmonary complications were not significantly different (Table 2).

Cardiac complications in the matched groups

Cardiac complications consisted almost exclusively of arrhythmias and occurred in 20 (20.8%) patients in group 1 versus 33 (34.4%) in group 2, which was significantly different (p = 0.036). Time between the end of neoadjuvant CRT and surgery seemed to have no influence on the development of postoperative arrhythmias (52 days vs. 54 days; p = 0.676). Also in the unmatched cohort, arrhythmias were significantly more observed in the group treated with neoadjuvant CRT (p = 0.008).

Other complications in the matched groups

None of the other complications turned out to be significantly different between patients treated with surgery alone compared to patients treated with neoadjuvant CRT followed by surgery (Table 2).

Postoperative course

Despite a higher incidence of pneumonia, patients treated with neoadjuvant CRT had a slightly shorter median ICU stay (3.5 vs. 3.0 days; $p = 0.954$) and an identical in hospital stay (16.0 vs. 16.0 days; $p = 0.986$). The number of reoperations (6.3% versus 8.3%; $p = 0.579$) appeared to be similar as well.

Multivariate analysis

To determine the influence of neoadjuvant CRT on the development of postoperative complications, we performed a multivariate analysis for complications with a p-value < 0.1 in univariate analyses. Neoadjuvant CRT ($p = 0.001$, odds ratio (OR): 2.896) and side of thoracotomy, at the prejudice of a right-sided approach ($p = 0.020$, OR: 2.134) were significantly associated with the development of pneumonia. Pleural effusion was associated with neoadjuvant CRT ($p = 0.041$, OR: 2.268) and side of thoracotomy ($p = 0.004$, OR: 3.951). Risk factors for arrhythmias were neoadjuvant CRT ($p = 0.023$, OR: 2.215) and age ($p = 0.000$, OR: 1.084) (Table 3).

Multivariate analysis in the unmatched data revealed similar results. In comparison to the matched data, neoadjuvant CRT ($p = 0.001$, OR: 2.333) and side of thoracotomy at the prejudice of a right-sided approach ($p = 0.009$, OR: 1.906) were associated with the development of pneumonia. Pleural effusion was not significantly associated with neoadjuvant CRT in the unmatched data, but with heart failure ($p = 0.010$, OR: 8.414), history of

Table 3. Significant outcomes in multivariate analyses

Matched data	Pneumonia		Pleural effusion		Arrhythmias	
	OR	95% CI	OR	95% CI	OR	95% CI
Neoadjuvant CRT	2.896	1.566-5.357	2.268	1.035-4.969	2.215	1.114-4.403
Side of thoracotomy	2.134	1.127-4.042	3.951	1.540-10.141	-	-
Age	-	-	-	-	1.084	1.037-1.133
Unmatched data						
Neoadjuvant CRT	2.333	1.423-3.826	-	-	2.503	1.426-4.395
Side of thoracotomy	1.906	1.179-3.081	2.433	1.221-4.848	-	-
Heart failure	-	-	8.414	1.670-42.391	6.690	1.197-37.389
History of smoking	-	-	1.890	1.008-3.544	-	-
Age	-	-	-	-	1.066	1.032-1.101

smoking (p = 0.047, OR: 1.890), and side of thoracotomy at the prejudice of a right-sided approach (p = 0.011, OR: 2.433). Finally, arrhythmias were associated with neoadjuvant CRT (p = 0.001, OR: 2.503), age (p = 0.000, OR: 1.066), and in contrast to the matched data, also with heart failure (p = 0.030, OR: 6.690).

DISCUSSION

Current study demonstrates an increased incidence of postoperative pneumonia, pleural effusion, and arrhythmias by approximately twofold after the introduction of neoadjuvant chemoradiotherapy. Although these outcomes suggest an increased risk for prolonged ICU and/or hospital stay or even mortality risk, this was not confirmed by present data.

After the positive impact of neoadjuvant CRT in the multicenter randomized CROSS trial, the acceptance in daily management has increased for the current used regimen of radiotherapy with concurrent carboplatin and paclitaxel to improve overall survival [2]. However, the role of CRT prior to the esophagectomy has been debated for several decades. Part of this prolonged discussion was the occurrence of toxic cardiopulmonary adverse events and consequently a raised postoperative risk for morbidity and mortality [6]. Besides cardiopulmonary complications, inflammation and anastomotic leakage were also feared [8].

The pathophysiological correlation between radiation dose to the lungs and the risk of pulmonary complications has been demonstrated by several studies [17, 18]. Wang *et al.* found that the volume of the lung spared from doses of ≥ 5 Gy was the only independent dosimetric factor for the risk of postoperative pulmonary complications (defined as pneumonia or ARDS). This suggests that a lower dose of radiotherapy in a multimodality treatment leads to a minimization of irradiated lung volume and might reduce the incidence of pulmonary complications. The radiation dose to the heart in the neoadjuvant setting of distal esophageal cancer is quite substantial, despite the relatively low total radiation dose. Radiation to the pericardium increases the risk of pericardial effusion, which seems to be dose-dependent [24]. Arrhythmia might display radiation-induced cardiac toxicity. However, little is known about the correlation between arrhythmia and radiotherapy in esophageal cancer patients. Moreover, paclitaxel may induce ventricular arrhythmias, bradycardia and several degrees of atrioventricular conduction blocks [25]. It is essential to reduce the amount of radiation on cardiopulmonary organs without compromising the beneficial effect of radiotherapy. Improvements of advanced radiation technologies using intensity modulated radiation therapy are promising and further research is warranted [26].

Conflicting data have been reported over the past years about the influence of neoadjuvant CRT on the postoperative course [2-8]. Merritt R.E. et al. concluded that major complications would not appear to increase due to neoadjuvant CRT, but were associated with the transthoracic approach and preoperative coronary artery disease [7]. Similar results were reported whereby neoadjuvant CRT did not appear to be an important predictor of major morbidity and mortality after esophagectomy, not even in elderly patients [4]. However, other reports did identify an increased incidence of pulmonary and septic complications after neoadjuvant CRT [6]. These different outcomes may be explained by considerable bias due to different neoadjuvant regimens in terms of dose or schedule for both chemotherapy and radiation. Chemotherapy based on cisplatin and/or 5-fluorouracil (5-FU) generally has more intense adverse side effects compared to the combination of carboplatin/paclitaxel [25, 27]. Additionally, there is a lack of uniformity in postoperative definitions and comparison of non-homogeneous groups without any correction for differences in surgical approach [28].

Besides uncertain effects of neoadjuvant CRT in developing postoperative complications, there is still doubt about the “ideal time period” after preoperative CRT and surgical resection. In this study, although it was not our main purpose, we could not demonstrate any correlation between these variable and postoperative complications. In rectal cancer, delayed surgery beyond 8 weeks after neoadjuvant CRT seemed to reduce postoperative morbidity without compromising prognosis [29].

Although significantly different between both groups, the cardiopulmonary complications in this study seemed to be relatively high. This might be explained by the fact that all patients underwent a transthoracic esophagectomy, which has a relatively higher morbidity and/or mortality rate [7]. Moreover, we used comprehensive definitions for postoperative complications, but the incidence of postoperative morbidity did not result in an increased mortality.

Awareness of clinicians could reduce postoperative complications when treatment is started earlier or even immediate postoperative as a preventive strategy [30, 31]. Currently, neoadjuvant CRT is given in our institution to patients with a comparable conditional status as was based on the inclusion criteria of the CROSS trial. Patients with a considerable frailty during pre-treatment assessment are excluded for neoadjuvant CRT. Indeed, our results underline a cautious use of neoadjuvant CRT in this group of patients, given the increased risk of cardiopulmonary complications. Therefore, we make a plea for an individualized treatment strategy in which neoadjuvant CRT plays an important role. Unfortunately, an objective measurement to properly assess the condition of the patient is still missing [23].

CONCLUSION

This study shows an increased incidence of pneumonia, pleural effusion and arrhythmia after neoadjuvant chemoradiotherapy, without increasing the mortality risk in the treatment of esophageal cancer patients. In multivariate analysis neoadjuvant chemoradiotherapy was significantly associated with the risk of pneumonia and arrhythmia. Further research should be focused on limitation of chemoradiotherapy-induced cardiopulmonary toxicity.

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5

Early routine blood analyses within 48 hours after esophagectomy may reflect short-term outcome in patients with esophageal cancer

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ABSTRACT

Introduction: To reduce the severity of postoperative (p.o) complications after esophagectomy in esophageal cancer (EC) patients, early identification is of great importance. We evaluated the prognostic value of early (< 48 hrs) p.o routine peripheral blood measurements for complications during hospital stay and short-term mortality (< 90 days) after transthoracic esophagectomy (TTE).

Methods: Between 2006 and 2012, blood samples of 210 EC patients were analyzed on three consecutive time points: 0 (T1), 24 (T2) and 48 (T3) hours after resection for albumin (Alb), creatinine, C-reactive protein (CRP), lactate dehydrogenase (LDH), white blood cell count (WBC), platelet count and hemoglobin (Hb). Multivariate analysis was performed on factors with p-values ≤ 0.1 at univariate analysis. Significant results were further analyzed by applying an area under the Receiver Operator Curve (AUC) to determine discriminatory power.

Results: Sepsis and anastomotic leakage were moderately predicted by LDH at T2 (OR: 1.012; AUC: 0.71 and OR: 1.008; AUC: 0.71 respectively), whereas CRP at T3 was associated with sepsis (OR: 1.008; ROC: 0.72). Renal failure was strongly associated with creatinine at T2 (OR: 1.039; ROC: 0.74). Short-term mortality (N = 12) was assessed by creatinine (T2) (OR: 1.020), but without discriminatory power (0.52).

Conclusion: Early derangements of LDH (T2), creatinine (T2) and CRP (T3) may be helpful in timely detection of serious complications after esophagectomy.

INTRODUCTION

In the last three decades and particularly in elderly patients, a rising incidence of esophageal cancer (EC) has been observed, resulting in the 7th most commonly diagnosed malignancy worldwide[1]. For patients presenting with localized disease, surgery, usually after neoadjuvant chemoradiotherapy (CRT), remains important in achieving potentially curative treatment. Even though postoperative mortality has decreased, this major surgical procedure is associated with substantial perioperative morbidity (40-60%) and in-hospital mortality (3-5%)[2, 3]. Postoperative complications are mainly pulmonary related, ranging from pneumonia to acute respiratory failure, or infectious from other origins[4, 5]. Neoadjuvant CRT seems to increase the susceptibility of both pulmonary and inflammation related complications[6].

It is important to identify early signs of a potentially complicated postoperative course after esophagectomy, which could lead to a more effective management with eventually lower mortality and shorter stay at the intensive care unit (ICU)[7]. Currently available individual risk stratifications are not reliable enough to be used in established pathways of care and in guiding clinical decision-making[7]. However, comprehensive clinical and biological parameters together may increase the awareness which could be useful in timely treatment decisions.

Several studies analyzed the value of routine blood examination to predict postoperative outcome as the result of both surgical trauma and preoperative patient-related risk factors[8-16]. Complement activation and acute phase response induced by surgery, with marked decrease levels of albumin and elevated levels of C-reactive protein (CRP) in the first postoperative days was shown to contribute to postoperative morbidity[8, 17]. However, data on the value and degree of deviation of postoperative routine blood tests and the association with other putative interfering factors in predicting postoperative complications and mortality are scarce or inconsistent. A correct interpretation of abnormal blood tests after esophagectomy could result in a better insight of the postoperative course in EC patients. In this study we analyzed the correlation between early routine peripheral blood values and the occurrence of postoperative morbidity and short-term mortality after esophagectomy.

PATIENTS AND METHODS

Patients

Between 2006 and 2012, 210 consecutive EC patients underwent a surgical resection with curative intent. In a prospectively maintained database, the following data was included;

demographic information, neoadjuvant treatment, tumor characteristics, therapeutic information, complications and survival data. For the analysis, relevant data was entered into a separate, anonymized database according to the rules of our Institutional Review Board (www.ccmo.nl)

Neoadjuvant Chemoradiotherapy and surgery

Since 2006, neoadjuvant CRT consisted of carboplatin and Paclitaxel, with concurrent radiotherapy of 41·4 Gy in daily fractions of 1·8 Gy, five times per week was applied in patients with tumors staged as T1N1-3 or T2-T4aN0-3 without distant metastases (CROSS regimen) [18].

All patients underwent a transthoracic esophagectomy (TTE) with two-field lymphadenectomy by two experienced surgeons, in a tertiary referral center. Tumors around the gastro-esophageal junction were generally approached through a left thoraco-laparotomy with intrathoracic anastomosis, while more cranially located esophageal tumors were approached through a right sided thoracotomy with cervical anastomoses. Patients went postoperatively to the ICU, where they were usually extubated within 24 hours after surgery.

Routine peripheral blood tests

After surgery, EDTA blood samples were taken on routine base. For this study we evaluated seven measurements drawn in each patient up to 48 hours postoperatively at three different time points: immediately after surgery on arrival at the ICU (T1), ≥ 24 hours (T2) and ≤ 48 hours (T3) after surgery. We evaluated a total of 3850 blood values, with 560 missing values, which were distributed randomly. The following routine serum blood measurements were analyzed; hematological function tests (white blood cell count (WBC), platelet count (PC) and hemoglobin (Hb)); inflammatory reactions (C-reactive protein: CRP), albumin (Alb) and lactate dehydrogenase (LDH)); renal function test (creatinine, which is also a measure of muscle mass) and liver function tests (levels of LDH and Alb).

Definitions of outcome

The primary endpoints were early postoperative morbidity and short-term mortality. For a real estimation of postoperative mortality after esophagectomy, we defined short-term mortality as death within the first 90 days after surgery and/or within the same hospital admission. Postoperative complications were identified and classified as follows: Pulmonary complications were defined as: pneumonia (infiltrate on X-ray with positive sputum culture or antimicrobial therapy on clinical indications), respiratory failure (ICU re-admission for respiratory support and/or re-intubation), and acute respiratory distress syndrome (ARDS: acute and persistent lung inflammation with increased vascular permeability, bilateral infiltrates on x-ray and severe hypoxemia requiring the need for mechanical ventilation). Infectious complications were defined as: sepsis (clinical signs of SIRS, but with culture-proven infection or infection identified by visual inspection), anastomotic leakage (on oral contrast esophagography or CT and elevated amylase in drainage pleural fluid), renal failure (i.e. rising creatinine and oliguria requiring renal replacement therapy), Cardiac complications; arrhythmia (diagnosed on ECG).

Statistics

Results were presented as frequencies, means or medians with percentages and interquartile range. Odds ratios (OR), confidence intervals (CI) and *p*-values between serum values and morbidity/mortality rates were determined with univariate logistic regression analysis. Significant outcomes with a threshold of p-value of ≤ 0.1 were further analyzed with multivariate analysis through a backward selection and area under the Receiver Operator Curve (AUC) to determine discriminatory power. Values between 0.7-0.8 suggest moderate discrimination and values exceeding 0.8 suggest good discrimination. Statistical analyses were performed by using the statistical package of SPSS version 20.0.0 (SPSS Inc., Chicago, IL USA).

RESULTS

Clinical characteristics, co-morbidities and complications after esophagectomy are summarized in Table 1. Median age was 64.1 (range: 34.7-85.1) years. Almost half of the patients in this cohort received neoadjuvant CRT (96 patients; 45.7%). As depicted, many patients suffered from cardiovascular comorbidities. Most common postoperative complications were cardiopulmonary-related; 89 patients (42.4%) suffered from pneumonia, 45 (21.4%) had respiratory failure and 51 (24.3%) developed arrhythmia. Short-term mortality, including in-hospital and < 90-day mortality, was 5.7% (N = 12).

Routine blood values and cardio-pulmonary complications

In addition to a number of laboratory parameters, age, neoadjuvant CRT, co-morbidity, smoking and side of thoracotomy were associated at p-value < 0.1 in the univariate analyses. After multivariate logistic regression analysis, postoperative albumin concentrations (T1) (OR: 0.913; 95% confidence interval (CI): 0.851-0.979) and neoadjuvant CRT (OR: 2.127; CI: 1.157-3.909) were independent prognostic factors in developing pneumonia (Table 2). However, albumin at T1 had no discriminatory power in ROC analysis (0.63; CI: 0.55-0.71). In predicting respiratory failure, only a right sided thoracic approach was significantly associated (OR: 2.251; CI: 1.040-4.871).

Table 1. Patients characteristics, preoperative co-morbidity and complication rates after esophagectomy: N = 210 (%)

Characteristics (%)		**Comorbidity (%)**		**Complications (%)**	
Mean age (yrs)	64.1	Diabetes mellitus	28 (13.3)	Pneumonia	89 (42.4)
Sex (M/F)	162/48	Heart failure	4 (1.9)		
Histology		Myocardial infarction	25 (11.9)	Respiratory failure	45 (21.4)
Adenocarcinoma	172 (81.9)	COPD	22 (10.5)		
Squamous cell ca.	37 (17.6)	Smoking	85 (40.5)	ARDS	5 (2.4)
Other	1 (0.5)			Pulmonary complications	101 (48.1)
Localization		**ASA classification**		Sepsis	17 (8.1)
Mid esophagus	37 (17.6)	ASA 1	13 (6.2)	Leakage	21 (10.0)
Distal esophagus	141 (67.1)	ASA 2	116 (55.2)	Renal failure	8 (3.8)
GEJ	32 (15.2)	ASA 3	51 (24.3)	Infectious complications	40 (19.0)
Neoadjuvant CRT		ASA 4	2 (1.2)	Arrhythmias	51 (24.3)
Yes/No	96/118	Missing	28 (13.3)	Re-operation	13 (6.2)
Thoracotomy				Re-admission ICU	36 (17.1)
Left/right	99/111			Short-term mortality: ≤ 90 days	12 (5.7)
				30-day mortality	7 (3.3)

GEJ: Gastroesophageal Junction. COPD: Chronic Obstructive Pulmonary Disease. ARDS: acute respiratory distress syndrome. ASA: American Society of Anesthesiologists

Table 2. Multivariate analysis of complications, only significant results in multivariate logistic regression are displayed. OR (95% CI)

	Pneumonia	**Respiratory failure**	**Arrhythmias**	**Renal failure**
Albumin T1	0.913 (0.851-0.979)			
Creatinine T2				1.039 (1.016-1.062)
Age			1.094 (1.039-1.153)	
Neoadjuvant CRT	2.127 (1.157-3.909)		4.738 (1.902-11.802)	
Myocardial infarction			0.076 (0.007-0.838)	
COPD			5.312 (1.688-16.719)	
Smoking			2.790 (1.204-6.465)	
Side of thoracotomy		2.251 (1.040-4.871)		
	Sepsis	**Leakage**	**Re-admission ICU**	**Short-term mortality**
Creatinine T2				1.020 (1.001-1.039)
CRP T3	1.008 (1.001-1.016)			
LDH T2	1.012 (1.003-1.021)	1.008 (1.001-1.016)	1.006 (1.001-1.012)	
COPD	4.879 (1.089-21-869)			
Smoking				10.84 (1.97-59.50)
Side of thoracotomy				5.49 (1.00-30.07)

Arrhythmias were only predicted by preoperative patient and treatment-related factors including; age (OR: 1.094; CI: 1.039-1.153), neoadjuvant CRT (OR: 4.738; CI: 1.902-11.802), myocardial infarction (OR: 0.076; CI: 0.007-0.838), COPD (OR: 5.312; CI: 1.688-16.719), and smoking (OR: 2.790; CI: 1.204-6.465) (Table 2).

Routine blood values and infectious complications

Sepsis was associated with elevated levels of CRP at T3 (OR: 1.008; CI: 1.001-1.016) with moderate discriminatory power (0.72; CI: 0.61-0.83) (Table 2 and Figure 1) and LDH at T2 (OR: 1.012; CI: 1.003-1.021; AUC: 0.71; CI: 0.57-0.85) (Table 2 and Figure 2). In addition,

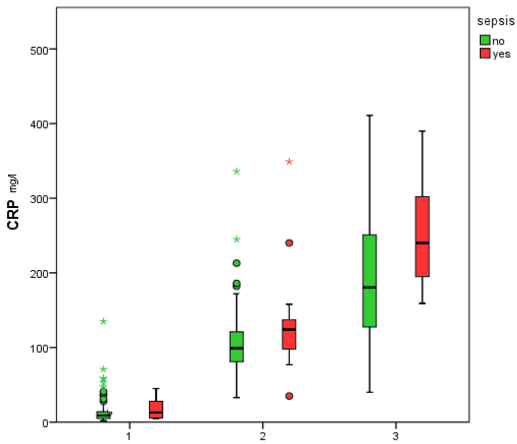

Figure 1. Postoperative sepsis and CRP (mg/l) concentrations on three time points

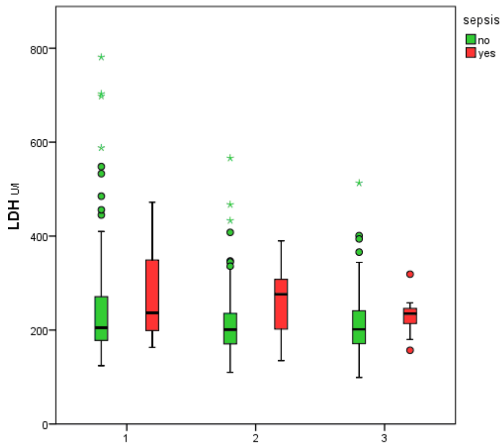

Figure 2. Postoperative sepsis and LDH (U/l) concentrations on three different time points

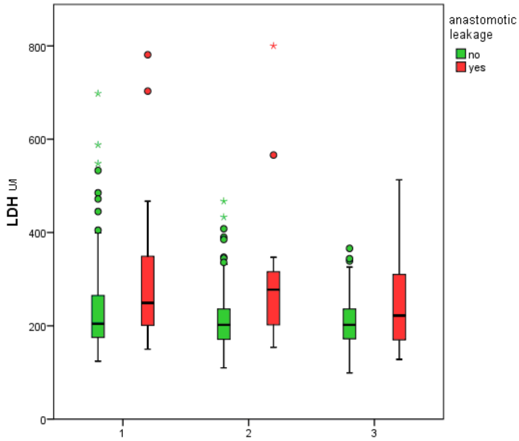

Figure 3. Postoperative anastomotic leakage and LDH (U/l) concentrations on three different time points

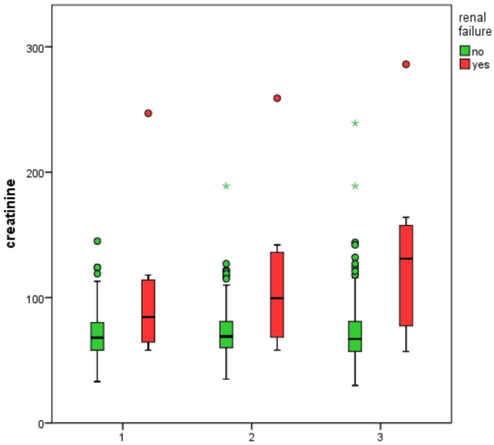

Figure 4. Postoperative renal failure and creatinine (µmol/l) concentrations on three different time points

LDH was also an independent prognostic marker in the event of anastomotic leakage (T2) (OR: 1.008; CI: 1.001-1.016; AUC: 0.71; CI: 0.54-0.88) (Table 2 and Figure 3). Renal failure was strongly associated with creatinine (T2) (OR: 1.039; CI 1.016-1.062; AUC: 0.74; CI: 0.52-0.95) (Table 2 and Figure 4).

Routine blood values and postoperative course/short-term mortality

Patients, who were re-admitted at the ICU, were predicted by elevated levels of LDH at T2 (OR: 1.006; CI: 1.001-1.012) (Table 2). Independent prognostic values for short-term mortality (in-hospital or within 90 days) were creatinine at T2 (OR: 1.020; CI: 1.001-1.039), side of thoracotomy to the detriment of a right-sided approach (OR: 5.49; CI: 1.00-30.07), and smoking (OR: 10.84; CI: 1.97-59.50) (Table 2). However, these peripheral blood measurements showed to have insufficient discriminatory power in ROC analysis.

Patients with neoadjuvant CRT had significantly lower levels of creatinine (p = 0.003 mean: 70,20 vs. 76,68), LDH (p = 0.029 mean: 218,28 vs. 238,07), WBC (p = 0.000 mean: 11,24 vs. 14,03), and platelet counts (p = 0.000 mean: 202,89 vs. 226,48). Besides, as previously described, neoadjuvant CRT was an independent prognostic marker for developing postoperative pneumonia and arrhythmias.

DISCUSSION

In improving quality of care, a better understanding in patient's response to surgical trauma, which might affect survival and postoperative complications, is essential. By focusing on the first 48 hours after esophagectomy, we intended to increase the awareness by providing additional tools in early identification of postoperative complications, even before they were clinically manifest. In the present study, deranged measurements of LDH, creatinine and CRP showed to be of independent prognostic value and with sufficient discriminatory power in predicting serious postoperative complications after esophagectomy.

Most centers in the Western world will determine these examined measurements daily in the first postoperative days. However, the interpretation of deranged values is difficult in clinical practice. Besides, major complications may interact with different physiological mechanisms, resulting in various deranged laboratory values. The wide range of different significantly predicted postoperative complications underlies the non-specificity of these measurements.

Albumin was in current study in multivariate analysis associated with pneumonia, however with insufficient discriminatory power. Generally albumin concentrations lower than 25 g/l, are associated with postoperative pulmonary complications[8]. Serum albumin levels rapidly decrease as part of the acute phase response and its association with postoperative complications may reflect as a marker of both malnutrition and the severity of host inflammatory response to the surgical insult[16]. Serum CRP and albumin levels, as incorporated into the Glasgow Prognostic Score, have shown to be an adequate prognosticator in different types of cancer[19, 20].

Induced by proinflammatory cytokines, CRP is mainly synthesized in hepatocytes but it can also be produced by many other cell types, including liver and lung macrophages, mononuclear cells and vascular endothelial cells[17]. The relatively high postoperative levels of CRP after a TTE are a part of a massive and immediate activation of the innate immunological response. However, it is difficult to distinguish between normal and abnormal elevated CRP levels. However, in current study, the increased CRP levels compared to baseline values after 48 hours were related to infectious (i.e septic) complications. These results correspond to previous research, in which increased levels of CRP were associated with postoperative complications[10]. In a study of Noble et al., combined values of albumin, CRP and WBC were related to the development of anastomotic leakage, but only after the third postoperative day[11]. Since we analyzed up to 48 hours postoperatively, we could not confirm these outcomes. Instead, we found that anastomotic leakage was associated with raised LDH concentrations. This intracellular enzyme is present in all cell types and elevated LDH levels are measured in a wide variety of conditions. LDH may be also a useful marker to provide important information about ongoing cellular damage, such as in anastomotic area after revascularization. But further research is warranted to confirm this hypothesis.

In daily practice, creatinine is a fairly reliable indicator of renal function. In EC patients, preoperative elevated creatinine levels were associated with pulmonary complications and anastomotic leakage[15, 21]. And indeed a rising postoperative creatinine concentration reflects a poor hemodynamic condition, which makes it a strong prognostic marker.

In the treatment of EC patients, neoadjuvant CRT was found to be responsible for a more aberrant postoperative course[6, 22]. It probably induces a more pronounced influence on immunological function than surgery alone and should be part of further research[23]. In relation to peripheral blood values, neoadjuvant CRT was associated with decreased levels of creatinine, LDH, and hematopoietic changes. Other important patient- and treatment related conditions in predicting postoperative complications were: smoking and side of thoracotomy.

Consequently, abnormal laboratory measurements after esophagectomy could be expected due to malnutrition, co-morbidity, neoplasm, age, neoadjuvant therapy and surgery-related conditions. In continuation with other studies in identifying complications early in the postoperative course, our observations indicate a more aberrant biochemical response in patients with postoperative morbidity and/or mortality. Moreover, we focused on the first 48 hours after esophagectomy to avoid bias resulting from blood sampling for specific complications or indications.

In conclusion, adequate interpretation of early deranged laboratory values after esophagectomy remains difficult, but could indicate for a more aberrant postoperative course. Clinicians should be aware of postoperative complications in patients with deranged levels of LDH, creatinine, and CRP, since these measurements could support early decision-making.

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Longitudinal analysis of cytokine expression during the different phases in the multimodal treatment of esophageal cancer patients

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Submitted

ABSTRACT

Objective: We aimed to provide prognostic value for cytokines concentrations on the degree of pathological response after neoadjuvant chemoradiotherapy (CRT) and occurrence of complications caused by either CRT or subsequent surgery at different time points in esophageal cancer (EC) patients.
Summary background data: Both CRT and subsequent esophagectomy are associated with release of multiple cytokines. This study provides more insight in the role of a number of cytokines throughout different phases in the multimodal treatment of EC patients.
Patients and methods: In a prospective observational study, 35 patients treated with platinum-based neoadjuvant CRT followed by transthoracic esophagectomy were included. Nine different cytokine concentrations were determined during the combined therapy of neoadjuvant CRT with subsequent surgery and in the first postoperative week.
Results: Intestinal fatty acid binding protein (I-FABP) increased (36 vs. 194 pg/ml; $p < 0.001$) during neoadjuvant CRT, but was not related to pathological response or complications. High concentrations of platelet activating factor (PAF) before and after neoadjuvant CRT were in ordinal logistic regression analysis associated with pathological response (OR: 0.202; $p = 0.006$, respectively OR: 0.434; $p = 0.015$). Angiopoietin 1 (Ang-1) after neoadjuvant CRT (OR: 0.382; $p = 0.006$), during surgical resection (OR: 0.687; $p = 0.033$ and OR: 0.678; $p = 0.040$) and in the postoperative period (OR; 0.514; $p = 0.031$) was in multivariate analysis associated with postoperative complications.
Conclusion: The unexpected rise of I-FABP after CRT point to early gastrointestinal damage. High PAF concentrations before and after neoadjuvant CRT might have prognostic value for pathological response, whereas decreased Ang-1 concentrations could indicate postoperative complications.

INTRODUCTION

In esophageal cancer (EC) patients, a combined treatment of neoadjuvant chemoradiotherapy (CRT) followed by curative intended esophagectomy with two-field lymphadenectomy is now standard of care in most centers. The beneficial effect of neoadjuvant CRT is based on the radio-sensitizing effect of combined chemotherapy, which allows improved resectability and a pathological complete response (pCR) rate of 15-30%[12]. Previous studies suggest that the prognosis of patients with pCR after neoadjuvant CRT may not benefit from subsequent surgery, while surgery in patients with insufficient or no response may be moved forward[3, 4]. Identifying these patients could be of great interest in further individualizing treatment strategy. To date there are no useful biomarkers available related to the degree of tumor response, although some pro-inflammatory cytokines seem to play an active role[56, 7]. Induced immune response by preoperative CRT has been demonstrated to change the levels of several soluble mediators, including interleukin (IL) 6 or inflammatory lipid metabolites such as platelet activating factor (PAF), which are related with both tumor response to treatment and tumor progression[8-10]. Furthermore, cytokine concentrations through all phases of the multimodality treatment might be correlated with the occurrence of complications caused by either CRT or surgery[11].
Esophageal resection is associated with a considerable rate of postoperative morbidity (40-60%) and in-hospital mortality (3-5%)[12, 13]. This is partly due to extensive activation of leucocytes, macrophages and endothelial cells with enhanced expression and release of anti- and pro-inflammatory cytokines due to severe surgical trauma and the necessity of prolonged one-lung ventilation (OLV)[1415]. Patients with markers of increased systemic inflammation are known to have an increased risk for postoperative complications[16]. Although reported toxicity was acceptable during neoadjuvant CRT, the correlation of patient's immunologic response in a multimodality treatment with early complications after subsequent surgery is not clear yet[1].
In current study, we aimed to provide prognostic value for a number of cytokines with different pathophysiological mechanisms on the degree of pathological response on neoadjuvant CRT as well as the occurrence of complications caused by either CRT or subsequent surgery at different measure points. To our knowledge, this is the first longitudinal observational study that will give us more insight in immunological responses throughout different phases in the multimodal treatment of EC patients.

PATIENTS AND METHODS

Patients

Between November 2011 and April 2013, we prospectively included 35 patients with histologically proven EC selected for esophagectomy after approval by our multidisciplinary tumor board. Patient's characteristics are described in Table 1. All patients received routine clinical care and no intervention was done for this study. In total, 262 blood samples were collected, with 53 (17%) missing values divided hazardly over the time points. The protocol was approved by the institutional review board (METC 2010.374) and all patients provided written informed consent.

Study design

To identify potentially prognostic cytokines for pathological response on preoperative CRT and postoperative complications of subsequent surgery, we included cytokines with different pathophysiological mechanisms. These included the pro-inflammatory markers interleukin (IL) 1β, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and procalcitonin, and the anti-inflammatory cytokine IL-10. Furthermore, two cytokines reflecting to endothelial function, angiopoietin 1 (Ang-1) and platelet activating factor (PAF) were measured. As a marker of the integrity of the small and large intestine, we also measured the intestinal fatty acid binding protein (I-FABP) (Figure 1).
From all included patients, EDTA-serum samples (s) were obtained at nine predetermined time (T) moments (Figure 1); day 1, before neoadjuvant CRT (sT1), day 7 of CRT (sT2), prior before surgery (sT3), during two lung ventilation (sT4), during one lung ventilation (sT5), first (sT6), third (sT7), fifth (sT8), and seventh (sT9) postoperative day (Figure 1). Cytokine concentrations were determined by means of sandwich ELISA (Enzyme-Linked Immunosorbent Assay) based on capture and biotin-labelled detection antibodies. D Streptavidin-HRP and OPD substrate were used to quantify the amount of cytokines. Samples were diluted 1:1 in 0.1% BSA/PBS buffer, except for PAF, which was diluted 1:1000 in 0.1% BSA/PBS buffer.

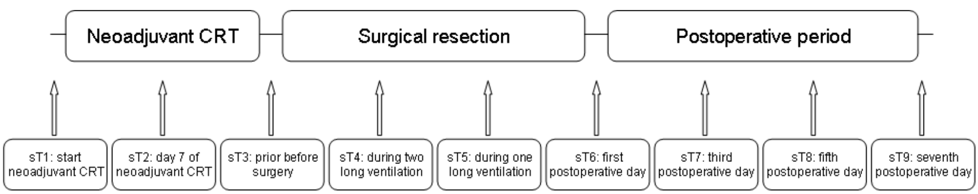

Figure 1. Timeline of sampling throughout different phases of treatment

Table 1. Patient's characteristics

Variable	**N = 35 (%)**
Age in years (median)	64.9
Sex (M/F)	30/5
Histology	
Adenocarcinoma	32 (91.4)
Squamous CC	3 (8.6)
ASA classification	
ASA I	5 (14.3)
ASA II	23 (65.7)
ASA III	7 (20.0)
Surgery	
TTE right sided	22 (62.9)
TTE left sided	13 (37.1)
Complications after neoadjuvant CRT	
Minor complications	15 (42.9)
Moderate complications	2 (5.7)
Pathological response*	
Mandard 1	4 (11.4)
Mandard 2	6 (17.1)
Mandard 3	13 (37.1)
Mandard 4	11 (31.4)
Mandard 5	1 (2.9)
Complications	
Respiratory failure	5 (14.3)
Pneumonia	17 (48.6)
Re-intubation	5 (14.3)
Arrhythmias	12 (34.3)
Sepsis	2 (5.7)
Anastomotic leakage	1 (2.9)
Postoperative complications	18 (51.4)
Surgical mortality**	3 (8.6)
Postoperative course	
Reoperation	2 (5.7)
OR-time (mean)	8.89 hrs
ICU-stay (median)	1.0 days
Hospital stay (median)	14.0 days

ASA: American Society of Anesthesiologists. * According to the Mandard Classification
** surg. mortality i.e both in hospital and 90-day mortality

Neoadjuvant chemoradiotherapy

Preoperative CRT consisted of carboplatin and paclitaxel with concurrent radiotherapy (CROSS scheme according to Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study[1]). Oncologic criteria consisted of a clinical tumor stage of T1N1-3 or T2-T4aN0-3 without distant metastases (M0), according to the 7th TNM AJCC edition. Carboplatin (AUC 2) and paclitaxel 50 mg/m2 were administered weekly for 5 weeks. Radiotherapy consisted of 41.4 Gy in daily fractions of 1.8 Gy, five times per week.

Surgery

Patients were planned for a surgical resection with curative intent, usually within 4-8 weeks after neoadjuvant CRT. All 35 patients underwent a transthoracic esophagectomy with two-field lymphadenectomy by two experienced surgeons in a high-volume center. All patients received orotracheal intubation using a double lumen tube for applying selective one-lung ventilation, which was based on pressure controlled ventilation with low tidal volumes (protective ventilation strategy). According to the protocol, all patients were intubated at transfer to the intensive care department, where they usually were detubated on indication and stay overnight.

Definitions of outcome

Pathological response to treatment was classified according to the commonly used Mandard classification varying from 1 (complete regression) to 5 (absence of regressive changes)[17]. Major pathological response was defined as Mandard 1, moderate as Mandard 2/3 and minor response as Mandard 4/5[18]. Complications from neoadjuvant CRT were scored according to the National Cancer Institute common toxicity criteria for adverse events (CTCAE version 4.03). Postoperative complications included pneumonia (defined as infiltration on X-ray, positive sputum culture, antimicrobial therapy for therapeutic purpose), respiratory insufficiency (prolonged need for mechanical ventilation, re-admission on the ICU for respiratory support and/or re-intubation), sepsis (the clinical signs of SIRS i.e. systemic inflammatory response syndrome with culture-proven infection or infection identified by visual inspection), and anastomotic leakage (CT with oral contrast and elevated amylase in drainage fluid). Surgical mortality was defined as either death during the same hospital stay (in-hospital mortality) or within the first 90 days after surgery. Severity of co-morbidity was classified according to the American Society of Anesthesiology (ASA) score varying from ASA 1 (very good condition) to ASA 5 (moribund patient).

Statistics

Results were presented as frequencies with percentages, means or medians. To determine the effect of different interventions on cytokine concentrations, changes after neoadjuvant CRT (sT1 vs. sT3), surgery (sT3 vs. sT6) and in the postoperative course (sT6 vs. sT9) were analyzed with a paired sample *t*-test (normal distribution of the changes) or Wilcoxon signed rank test (skewed distribution). Furthermore to determine clinical consequences, cytokine concentrations on sT1, sT2, and sT3 were in univariate analyses related to the three degrees of pathological response and complications after neoadjuvant CRT. In addition, all time points were assessed whether they were associated with postoperative complications and outcomes with a p-value < 0.10 were further analyzed with multivariate logistic regression analysis and corrected for age, histology, cT-stage, ASA classification, and type of surgery. A p-value < 0.05 was considered to be significant. Statistical analyses were performed by using the Statistical Package for Social Sciences: SPSS version 20.0.0 (SPSS Inc., Chicago, IL USA).

RESULTS

Major pathological response was observed in 11.4% (Mandard 1: N = 4), while 12 patients (34.2%) had minor or no response at all (Mandard 4/5; Table 1). Mild complications from neoadjuvant CRT occurred in 15 patients (42.9%), and two patients (5.7%) suffered from moderate complications (both thromboembolic process). More than half of this cohort suffered from postoperative complications (51.4%) (Table 1).

1. Cytokine concentrations during neoadjuvant CRT

Enhanced concentrations of I-FABP were observed during neoadjuvant CRT and showed to be significantly higher after neoadjuvant CRT (36.1 pg/ml vs. 193.9 pg/ml; p < 0.001) (Table 2). Remarkably, these elevated concentrations could not be related in univariate analysis to the degree of pathological response or complications after neoadjuvant CRT or surgery.
Ang-1 concentrations between sT1 and sT3 were not significantly different (3.4 ng/ml vs. 3.9 ng/ml; p = 0.338) (Table 2, Figure 2). Nevertheless, a low concentration of Ang-1 after

Table 2. Paired sample analysis in cytokine concentrations on different time points (mean)

	sT1 (N = 26)	sT3 (N = 26)	p-value	sT3 (N = 27)	sT6 (N = 27)	p-value	sT6 (N = 24)	sT9 (N = 24)	p-value
Ang-1 (ng/ml)	3.4	3.9	0.338	4.1	4.5	0.455	4.2	4.5	0.532
I-FABP (pg/ml)	36.1	193.9	**0.000**	212.7	56.3	**0.000**	50.5	35.4	0.494
IL-1β (pg/ml)	14.5	13.9	0.702	15.6	14.3	0.700	29.8	25.9	**0.032**
IL-6 (pg/ml)	20.3	15.5	0.687	23.5	489.4	**0.000**	377.7	204.8	**0.018**
IL-8 (pg/ml)	7.7	12.0	0.055	12.6	6.7	0.355	11.3	9.6	0.560
IL-10 (pg/ml)	32.8	46.0	0.581	50.6	62.2	**0.009**	62.8	38.5	**0.022**
Procalcitonin (pg/ml)	4.7	4.4	0.983	4.3	104.9	**0.000**	106.2	10.3	**0.000**
PAF (ug/ml)	4.8	5.3	**0.046**	5.3	4.7	**0.024**	4.6	5.2	**0.013**
TNF-α (pg/ml)	62.8	58.6	0.989	62.9	66.8	0.442	83.8	51.4	**0.001**

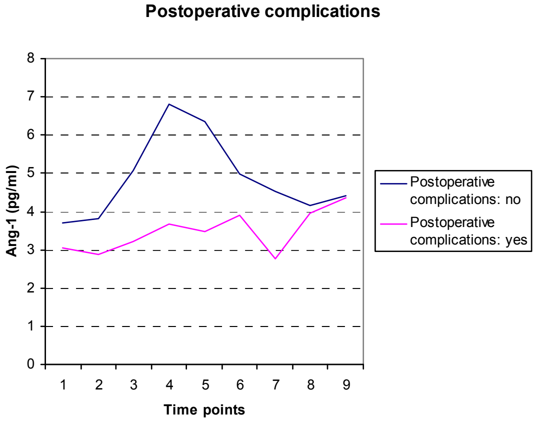

Figure 2. Ang-1 concentrations (mean) related to postoperative complications throughout different phases of the treatment

neoadjuvant CRT (sT3) was associated with more severe postoperative complications in multivariate logistic regression analysis (odds ratio (OR): 0.382; 95% confidence interval (CI): 0.193-0.758; p = 0.006).

Concentrations of PAF were significantly elevated at the end of neoadjuvant CRT (4.8 ug/ml vs. 5.3 ug/ml; p = 0.046) (Table 2). A sustained relatively high PAF concentration at the start and after neoadjuvant CRT was in multivariate ordinal regression analysis associated with major pathological response (OR: 0.202; 95% CI: 0.064-0.636; p = 0.006 and OR: 0.434; 95% CI: 0.241-0.782; p = 0.015 respectively) (Figure 3). When analyzing

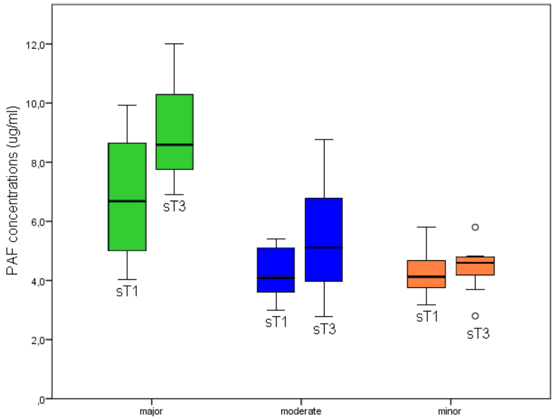

Figure 3. PAF sT1 and sT3 concentrations (ug/ml) related to major, moderate and minor pathological response

each degree of pathological response, only PAF concentrations after neoadjuvant CRT in patients with major pathological response were significantly elevated (mean sT1: 7.3ug/ml vs. sT3: 9.1 ug/ml; $p = 0.001$).
Although IL-1β concentrations decreased during neoadjuvant CRT, none of the IL concentrations (1β, 6, 8, or 10), nor TNF-α or procalcitonin were statistically different between sT1 and sT3 or associated neither with the degree of tumor response nor with postoperative complications (Table 2). None of the examined cytokines were associated with complications during neoadjuvant CRT.

2. Cytokine concentrations during surgery
The surgical insult was responsible for large variations in most of these cytokines. Significantly elevated concentrations after surgical resection (sT3 vs. sT6) were observed for IL-6, IL-10, and procalcitonin. In assessing the effect of two and lung ventilation on cytokine concentrations, differences between sT4 and sT5 were examined and only IL-6 turned out to be significantly different (mean: 87.79 and 347.90 respectively, $p = 0.021$). Concentrations of PAF and I-FABP were significantly decreased after surgical resection (Table 2). Of these cytokines, only Ang-1 was in multivariate logistic regression analysis (sT4 and sT5) related to postoperative complications (OR: 0.687; 95%CI: 0.486-0.970; $p = 0.033$ and OR: 0.678; 95%CI: 0.468-0.983; $p = 0.040$ respectively).

3. Cytokine concentrations in the postoperative period
Many of the deviating concentrations after surgical resection returned to normal in the first postoperative week. Concentrations of IL-1β, IL-6, IL-10, procalcitonin, and TNF-α decreased significantly between sT6 and sT9. Concentrations of PAF were rising in this postoperative period (Table 2). In univariate analysis, concentrations of Ang-1 on sT7 ($p = 0.014$), IL-6 on sT8 ($p = 0.008$) and sT9 ($p = 0.011$), and TNF-α on sT8 ($p = 0.040$) were associated with postoperative complications. However, in the multivariate logistic regression analysis, only Ang-1 was significantly associated with postoperative complications (OR; 0.514; 95%CI: 0.281-0.941; $p = 0.031$).

DISCUSSION

Neoadjuvant CRT is a crucial component in the curative treatment of EC patients. It has been demonstrated to improve both disease free and overall survival considerably after radical transthoracic esophagectomy[1]. However, both are accompanied by extensive tissue damage and stress related severe immunological response with activation of several cytokines and regulation of tumor receptor expression leading to either inhibition or stimulation of several growth factors and cell regulatory proteins[9, 10, 14]. A number of cytokines stimulate cell growth, including IL-1β and IL-6, while others induce or enhance toxicity during treatment (IL-6 and TNF-α), which triggers a cascade of inflammatory pathways[6, 8, 9, 19]. The clinical relevance of cytokine activation and its correlation with pathological response and complications caused by either CRT or subsequent surgery in a multimodal treatment is not clear yet. Based on these concerns, we aimed to provide prognostic value for a number of cytokines throughout different presupposed time points in the treatment of EC patients.

Systemic effects of both chemotherapy and radiotherapy induce pro-inflammatory responses through IL-1β, IL-6, IL-8, and TNF-α within hours after exposure[9, 20, 21, 19]. However, in the present data we could not demonstrate differences in concentrations in none of these cytokines. In fact, we observed significantly elevated concentrations of I-FABP and PAF after CRT. Measurement of I-FABP seemed to be related to chemotherapy-induced gastrointestinal (GI) mucositis, as was described by Derikx et al.[22]. They observed a rapid increase of I-FABP early after damage of the mucosal cell integrity. The increased concentrations of I-FABP that we observed, apparently originated from the damaged GI-tract, but could not be related to complications caused by CRT. The rapid decrease in the postoperative phase, even might suggest that the esophagus was the source of elevated I-FABP concentrations.

Besides significantly increased concentrations of PAF after neoadjuvant CRT, high PAF concentrations before and after CRT were associated with major pathological response. This may have clinical consequences, since these patients may not benefit from subsequent surgery, while curative intended esophagectomy in patients with insufficient or no response may be moved forward. Through binding to PAF receptor (PAF-R), PAF has been shown to activate several pathways such as nuclear factor-kappa B (NF-κB)[10, 23]. PAF-R can augment chemotherapy-induced effects through NF-κB dependent process, which is accompanied with the release of cytokines[10]. Furthermore, PAF is produced by various tissues and cell types and in response to different stimuli, including oxidative stress[23, 24]. Both chemo- and radiotherapy are potent pro-oxidative stressors and during tumors growth, many cells die by apoptosis or necrosis which is accompanied by oxidation of membrane phospholipids. These apoptotic cells express PAF-like molecules[23-25]. *Sakhi et al*. concluded that elevated levels of antioxidant biomarkers before radiotherapy and increased oxidative stress during radiotherapy may improve survival[26]. In the current study, we observed elevated PAF concentrations after CRT among all three groups (major, moderate and minor response), but only the major response group showed a significant difference. One of the possible explanations could be the release of PAF expressed by the massive amount of apoptotic tumor cells, while the initial response may be explained by NF-κB dependent process. However, we did not see an accompanying release of cytokines. Nevertheless, PAF concentrations could be of great importance and its association with pathological response needs to be confirmed in different cohorts before conducting with clinical consequences. In contrast to I-FABP and PAF, concentrations of Ang-1 could not be related to CRT administration, but were related to postoperative complications in different phases of the treatment. Angiopoietin (1 and 2) is a growth factor that specifically binds to the endothelial receptor tyrosine kinase Tie-2. Ang-1 mediated Tie2 signaling will lead to the maintenance of cellular integrity and quiescence of the endothelial barrier by covering the vessel with periendothelial cells whereas Ang-2 mediated Tie2 signaling will lead to the removal of these cells[27-29]. Decreased concentrations of Ang-1 are related to infectious complications[27, 28, 30]. Although Ang-1 concentrations were not significantly different between start and end of neoadjuvant CRT, extensive apoptosis of vascular endothelial cells affects endothelial function, including promotion of vessel maturation through angiogenesis[31]. Ang-1 in the current study might be negatively associated with the inflammatory response to surgery, which results in increased vascular permeability and inflammation. This might lead to early identifications of patients with a severe systemic inflammatory distress syndrome.

Cytokine alterations after transthoracic esophagectomy have been extensively described and investigated[22, 32, 33]. Surgical stress and the necessity of OLV is responsible for a massive release of pro-inflammatory cytokines and a depressed host immune response by T helper type 1 (Th1) and 2 (Th2) cells[1415]. In the current study, we observed increased IL-6 concentrations between conventional two-lung ventilation and OLV, but since surgery was continued over time, we were not able to determine the real effect of OLV alone. Despite protective ventilation strategy, OLV is associated with operative hypoxemia due to shunting of blood via the non-ventilated lung as well as surgery-induced compression[34]. Hypoxemia causes a release of pro-inflammatory cytokines, which might result in the development of postoperative acute respiratory distress syndrome[35]. Further reduction of pro-inflammatory response and hypoxemia during surgical resection might be achieved by applying high frequency jet ventilation, which has been demonstrated as a safe and adequate ventilation technique during esophagectomy[36].

Limited data is available about the influence of neoadjuvant CRT on cytokine production peri- and postoperatively[21, 37]. In rectal cancer patients a detrimental effect of preoperative CRT on postoperative cytokine release was demonstrated with depressed concentrations of IL-6 and TNF-α compared to patients without preoperative CRT[20]. In general, neoadjuvant therapy is assumed to reduce Th1 and Th2 cytokine production leading to prolonged T cell imbalance that extends beyond the time of surgery[21].

There are limitations in this study, since we included a relatively small number of patients. For this reason, coefficients in ordinal regression analysis may not be fully accurate and moreover, we did not correct our data for multiple testing. The results of this study should therefore be interpreted as a pilot, whereby deduced hypotheses need to be confirmed in a large cohort.

In conclusion, cytokine concentrations in particular PAF and Ang-1, in patients treated with neoadjuvant CRT followed by esophagectomy for EC seems to have prognostic value on the degree of pathological response (PAF) and occurrence of postoperative complications (Ang-1). Concentrations of I-FABP were increased considerably after neoadjuvant CRT indicating to early GI damage. More research is necessary before these cytokines can be considered as potentially useful prognostic markers.

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Summarizing discussion and future perspectives

Important improvements have been achieved in the past decades in staging and multimodality treatment of esophageal cancer (EC) patients[1]. Nevertheless, curative treatment for patients with EC remains challenging. Surgical resection, often preceded by neoadjuvant chemoradiotherapy (CRT), is still the mainstay of treatment with curative intent, but is also associated with considerable postoperative morbidity (40-60%) and mortality (3-5%)[2, 3]. Many patients are over 60 years of age and presenting with associated comorbidity, which has an important impact on treatment decision-making. Several patients and tumor-related factors determine treatment outcome, but there are unfortunately to date no objective measurements available for an adequate risk-assessment of EC patients.

The aim of this thesis was to identify different risk-factors for perioperative morbidity and mortality during different phases in the standard treatment of esophageal cancer patients, which could provide us an additional tool for a better selection of patients to different curative intended treatment options.

Chapter 2 describes the influence of age on postoperative outcome after an extended transthoracic esophagectomy with two-field lymphadenectomy. Elderly patients, defined as ≥ 70 years of age, were compared to younger patients for comorbidity, postoperative course, recurrent disease and survival. We concluded that age alone is not a sufficient prognostic indicator for short- and long-term outcome after esophagectomy. Despite a twofold increased risk of in-hospital mortality in elderly patients, we could not observe significant differences. And although overall complications were statistically comparable, cardiac complications such as arrhythmia, and pulmonary complications, especially atelectasis and respiratory insufficiency occurred more frequently in elderly patients. The presence of comorbidity was the strongest prognostic factor for the development of postoperative complications in this cohort. Moreover, long-term survival and recurrence rates were not related to the supposed disadvantage of elderly patients.
Both life expectancy and the incidence of EC are rising. Therefore, already in the near future, clinicians will be increasingly confronted with elderly patients with EC[4]. Denying surgery based on age alone seems not reasonable, but reticence is required in those with frailty due to co-morbidity, in particular based on cardiopulmonary dysfunction. In a review from 2013, authors concluded that elderly patients were at increased risk of pulmonary and cardiac complications, and perioperative mortality after esophagectomy[5].
Important improvements can be achieved in appropriate staging and selection of patients using optimal preoperative cardiopulmonary preparation. Severe pulmonary problems can be avoided by preoperative intensive muscle training and adequate epidural anesthesia.
Furthermore, different surgical approaches have been applied to reduce morbidity and mortality without diminishing the oncologic outcome. Currently, minimal invasive sur-

gery is propagated as the surgical method to reduce perioperative risk in these high-risk surgical patients, but large-scale randomized controlled trials are needed to confirm this assumption[6].

Since there is no adequate risk-prediction model in selecting patients for surgical resection, we attempted in **Chapter 3** to find the currently most accurate risk-prediction model for postoperative morbidity and mortality after esophagectomy. Therefore, five of the most frequently used risk-prediction models including P-POSSUM and O-POSSUM modifications, Charlson Comorbidity Index (CCI) and its Age Adjusted Charlson Score (ACCI) and the standard American Society of Anesthesiologists (ASA) classification, were evaluated. Although each of these risk-prediction models showed some relation between postoperative outcome and risk-score, we recommended O-POSSUM as individual risk stratification since it assessed the condition of the patient and the risk of surgery most accurately. For comparison between different cohorts, P-POSSUM was the most powerful predictor since it underestimated mortality by only one patient. For further applicability of clinical practice, we subdivided the O-POSSUM score in a low, intermediate and high-risk group. Despite these efforts, O-POSSUM is not generally used by clinicians, probably because of a lack of publicity. Instead, the most popular model of risk-assessment in daily practice is the ASA classification that excels in simplicity.
With multimodality treatment and a predominantly elderly population with considerable comorbidities, many factors could be associated with a complicated postoperative course. Therefore, identification of high-risk surgical patients remains difficult. With generally used ASA classification, we still have to deal with inter-observer dependent risk-assessment. With a more reliable score that realistically assess the magnitude of the therapy, we might even improve informed consent. Further research should be focused on already existing risk-adjusted models instead of developing new. In our opinion it is preferable to divide patients in risk-groups to improve informed consent and preoperative workup.

The incorporation of neoadjuvant CRT in the multimodality treatment of EC patients has dramatically increased in recent years. This is particularly due to the additional value of the Dutch national CROSS trial in which a significant survival benefit of 13% at 5 years after neoadjuvant CRT was demonstrated[1]. Although reported adverse events during neoadjuvant CRT were reported to be acceptable, other studies described an increased risk for thromboembolic toxicity as well as increased risk for postoperative complications[7-10]. **Chapter 4** describes the incidence and impact of preoperative and postoperative thromboembolic events (TEE) in EC patients. Patients with neoadjuvant CRT were matched with patients who were treated with surgery alone. In accordance to our hypothesis, neoadjuvant CRT was identified as an independent prognostic factor for developing TEE's in the preoperative phase, especially in those with a previous history of TEE. Postoperatively we could not demonstrate any differences in the incidence of TEE's between both groups. Although the majority of preoperative TEE's were idiopathic and diagnosed during a second re-staging CT-scan, we recommend secondary prophylaxis during neoadjuvant CRT in patients with a previous history of TEE. We base this recommendation mainly on a guideline published in 2007 of the American Society of Clinical Oncology[11]. However, prospective studies are needed to further define the use and safety of prophylactic therapy during platinum-based CRT in EC patients.

Other than the risk for a medical emergency, preoperative TEE's will inevitably interact with the postoperative course since anesthesiologists are more reluctant to administer epidural analgesia under anticoagulation. Adequate postoperative analgesia is important after esophagectomy, because postoperative pain compromises pulmonary function, coughing, and mobilization. Adequate epidural analgesia is associated with a reduced risk for pulmonary complications[12]. Appropriate prevention is necessary to avoid anticoagulatory therapy resulting in the use of other strategies than epidural analgesia. Nevertheless, despite of a significantly longer delay until surgery in patients with preoperative TEE's, we were not able to demonstrate any effect on the postoperative course.

Chemoradiotherapy prior for a radical esophagectomy might be associated with an increased risk for cardiopulmonary toxicity[13-15]. We evaluated in **Chapter 5** the effect of neoadjuvant CRT on postoperative morbidity and mortality in a matched cohort after esophagectomy. In multivariate analysis, neoadjuvant CRT was significantly associated with an increased risk for pneumonia and arrhythmia. Overall complications were comparable between both groups, which was in accordance to the CROSS trial[1]. In literature, conflicting data have been reported about the impact of neoadjuvant CRT on postoperative morbidity and mortality. However, the radiation exposure of heart and lungs during CRT is quite substantial and correlations between lower doses of radiotherapy are related to minimize the irradiation of the lungs[13]. Moreover, radiation to the pericardium might lead to an increased risk for pericardial effusion, which could be reflected in postoperative cardiac complications[16]. Therefore, further research should be focused on reduction of the amount of radiation on these organs, without compromising the beneficial effects of CRT. New and promising radiation techniques, such as proton beam therapy, could reduce cardiopulmonary toxicity.

Hospital volume is associated with improved short- and long-term outcomes in EC patients[17]. We hypothesized in a report (not included in this thesis) that surgeon-volume in a high-volume center is an additional independent prognostic factor for postoperative outcome after esophagectomy. In this report, we included two high-volume centers in the Netherlands and after multivariate analyses; surgeon volume was the only independent

prognostic factor for the development of anastomotic leakage. Since we aimed to include a great part of the northern located centers in the Netherlands, further research will be carried out to determine the effect of surgeon volume in a large multicenter trial.
The effect of open transthoracic esophageal resection on early postoperative peripheral blood values and their association with postoperative morbidity and mortality was evaluated in **Chapter 6**. A group of 210 consecutive EC patients underwent a radical transthoracic esophagectomy with curative intent. Standard peripheral blood values were acquired on three different time points with a maximum to 48 hours after resection. After multivariate analyses and ROC analysis, early deranged blood values of lactate dehydrogenase (LDH), creatinine, and C-reactive protein (CRP) were related to infectious complications after esophagectomy. Since major complications frequently interact with multiple pathophysiological mechanisms, complications of various etiologies were associated with different deranged peripheral blood values. This underscores the non-specificity of these measurements and the difficulty for a correct interpretation. Further research should be focused on more specific measurements to identify or predict postoperative complications in an early phase. Moreover, the pathophysiological mechanisms leading to a more aberrant postoperative course in patients is still not well understood. A better understanding and awareness might lead clinicians to start interventions earlier.

In **Chapter 7** we evaluated nine cytokines that reflect different (patho)physiological responses to better understand the innate immunological response throughout different phases in the multimodal treatment of EC patients. In this hypothesis-generating study, we included 35 patients and performed multivariate analyses to assess the degree of pathological response after CRT and complications caused by either CRT or subsequent surgery to identify prognostic value for these cytokines. Concentrations of intestinal fatty acid binding protein (I-FABP) were considerably increased after neoadjuvant CRT indicating gastrointestinal damage, since I-FABP is released in the case of a damaged integrity of mucosal cells[18]. Remarkably, I-FABP levels were far lower after surgery. High concentrations of platelet activating factor (PAF) before and after neoadjuvant CRT were related to major pathological response. Immunological pathways might also be responsible for augmentation of chemotherapy-induced effects of PAF through a nuclear factor-kappa B (NF-κB) dependent process[19]. Furthermore, apoptotic cells and oxidative stress can induce PAF and both radiotherapy and chemotherapy are known as potent oxidative stressors[20]. Finally we identified angiopoietin 1 (Ang-1) throughout different time points as an indicator of postoperative complications. Ang-1 is involved in the maintenance of cellular integrity and quiescence of the endothelial barrier of vascular cells[21]. A decreased Ang-1 concentration perioperatively could reflect an increased inflammatory response, which might result in vascular permeability[22]. Therefore, research should be focused on reduction of release of pro-inflammatory cytokines during surgical procedure. High frequency jet ventilation (HFJV) might contribute to a reduction of pro-inflammatory response, since this ventilation technique prevents patients from shunting of the non-ventilated lung and is accompanied by low tidal volumes. Moreover, HFJV has been demonstrated as a safe and adequate ventilation technique during esophagectomy[23]. Since we evaluated these cytokine concentrations in a relatively small group of EC patients, large prospective trials are needed to confirm our hypotheses.

In conclusion, with this thesis we aimed to contribute to the knowledge of several treatment related risk-factors in reducing perioperative morbidity and mortality in the standard curative treatment of esophageal cancer patients. Esophageal resection combined with neoadjuvant CRT should be initially considered in all medical fit and oncologically suitable patients. However, based on the outcomes of this thesis, clinicians should be aware of a complicated course due to side effects of CRT and patient and tumor-related characteristics. Individualizing treatment strategy remains an important target to improve quality of life and postoperative outcome.

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Nederlandse samenvatting

In het afgelopen decennium zijn belangrijke verbeteringen bereikt in de curatieve multimodale behandeling van patiënten met een slokdarmcarcinoom[1]. Vele patiënten met een slokdarmcarcinoom zijn ouder dan 65 jaar en hebben een of meerdere bijkomende aandoeningen (co-morbiditeit). Een curatieve behandeling van het oesofaguscarcinoom blijft daarom in vele gevallen uitdagend. Een chirurgische resectie van de slokdarm, vaak voorafgaand door neoadjuvante chemoradiotherapie (CRT), blijft de belangrijkste behandelmodaliteit, maar gaat vaak gepaard met een aanzienlijk risico op postoperatieve morbiditeit (40-60%) en mortaliteit (3-5%)[2, 3]. Tot op heden is het helaas onduidelijk welke risicofactoren bijdragen aan een gecompliceerd perioperatief beloop.

Het doel van dit proefschrift was om verschillende risicofactoren te identificeren die voorspellend zijn voor perioperatieve morbiditeit en mortaliteit gedurende verschillende fasen in de behandeling van patiënten met een slokdarmcarcinoom.

In **Hoofdstuk 2** beschrijven we de invloed van leeftijd op de postoperatieve uitkomst na een transthoracale slokdarmresectie. Oudere patiënten (gedefinieerd als 70 jaar en ouder) werden vergeleken met jongere patiënten met betrekking tot comorbiditeit, postoperatief beloop, optreden van recidieven en de lange termijn overleving. We concludeerden in dit onderzoek dat leeftijd geen onafhankelijke voorspellende factor is voor korte -en lange termijn uitkomst na een slokdarmresectie. Patiënten met een of meerdere comorbiditeiten hadden het hoogste risico op postoperatieve complicaties. Ondanks het ontbreken van een significant verschil, was het percentage oudere patiënten die in het ziekenhuis overleed ten gevolge van de operatie ruim twee keer zo hoog. Het totaal aantal postoperatieve complicaties tussen beide groepen was vergelijkbaar, maar cardiale complicaties (in het bijzonder hartritmestoornissen) en pulmonale complicaties (vooral atelectase en respiratoire insufficiëntie) kwamen vaker voor in oudere patiënten. Er was geen significant verschil in de lange termijn overleving en het aantal recidieven in oudere patiënten vergeleken met jongere patiënten. Gezien het feit dat de levensverwachting en de incidentie van slokdarmcarcinomen stijgt, zullen clinici vaker geconfronteerd worden met oudere patiënten[4]. Selecteren van patiënten voor een slokdarmresectie alleen gebaseerd op de leeftijd lijkt niet redelijk, maar terughoudendheid is vereist bij patiënten met comorbiditeit. Belangrijke verbeteringen zijn mogelijk in een adequate selectie en optimale preoperatieve cardiopulmonale voorbereiding[5]. Bovendien zou minimaal invasieve chirurgie kunnen bijdragen aan een verminderde perioperatief risico op morbiditeit en mortaliteit in risicovolle chirurgische patiënten[6]. Grootschalige gerandomiseerde studies zijn nodig om deze veronderstelling te bevestigen.

Tot op heden bestaat er geen goed model in het selecteren van chirurgische patiënten; het doel in **Hoofdstuk 3** was om vijf veelgebruikte risicomodellen, waaronder P-POSSUM, O-POSSUM, Charlson Comorbiditeit Index (CCI), de op leeftijd aangepaste Charlson Score (ACCI) en de American Society of Anesthesiologists (ASA) classificatie, te evalueren. Ondanks dat alle modellen in meer of mindere mate een redelijke voorspelling deden van het postoperatieve risico, concludeerden we dat O-POSSUM het meest nauwkeurige model was voor de individuele risico-inschatting. Voor de vergelijking tussen verschillende cohorten, bleek P-POSSUM de meest nauwkeurige voorspeller te zijn, omdat dit model de totale sterfte met slechts één patiënt onderschatte in ons cohort. Ter verbetering van de klinische toepasbaarheid, hebben we de O-POSSUM score onderverdeeld in een laag, gemiddeld en hoog risicogroep. Desondanks wordt de O-POSSUM score nog niet in de dagelijkse praktijk gebruik, mogelijk door een gebrek aan publiciteit. In plaats daarvan wordt de ASA classificatie frequent gebruikt, die uitblinkt in eenvoud.

Met de huidige multimodale behandeling kunnen meerdere factoren van invloed zijn op een gecompliceerd postoperatieve beloop. De identificatie van een risicovolle chirurgische patiënt blijft daarom moeilijk. Aangezien momenteel de ASA classificatie frequent gebruikt wordt, is de risico-inschatting onderhevig aan subjectieve waarnemingen. Daarnaast kan een eenduidige risicoanalyse die een realistisch beeld geeft van de omvang van de behandeling ook bijdragen aan een verbeterde *informed consent*. Verder onderzoek zou gericht moeten zijn op al bestaande risicoanalyse modellen. Naar onze mening zouden patiënten ingedeeld moeten worden in risico-groepen waarmee *informed consent* en preoperatieve voorbereiding verbeterd kunnen worden.

De invloed van neoadjuvante CRT in de multimodale behandeling van patiënten met een slokdarmcarcinoom is in de afgelopen jaren spectaculair toegenomen. Voor een deel is dit toe te schrijven aan een groot nationaal onderzoek (CROSS trial) waarbij de auteurs een significant overlevingsvoordeel van 13% hebben aangetoond na vijf jaar[1]. Ondanks dat de gerapporteerde bijwerkingen in dit onderzoek door CRT aanvaardbaar waren, hebben verschillende andere studies een verhoogd risico op trombo-embolische toxiciteit evenals een verhoogd risico op postoperatieve complicaties beschreven[7-10]. **Hoofdstuk 4** beschrijft de incidentie van pre -en postoperatieve trombo-embolische processen in patiënten met een slokdarmcarcinoom. In dit onderzoek werden patiënten met neoadjuvante CRT gematcht met patiënten die alleen een slokdarmresectie hadden ondergaan. In overeenstemming met onze hypothese, werd neoadjuvante CRT geïdentificeerd als een onafhankelijke prognostische factor voor de ontwikkeling van trombo-embolische processen in de preoperatieve fase en vooral bij patiënten met een belaste voorgeschiedenis voor trombo-embolische processen. De postoperatieve incidentie van trombo-embolische processen tussen beide groepen was gelijk. Ondanks dat de meerderheid van de preoperatieve trombo-embolische processen zonder klinische klachten gepaard gingen en bij toeval gediagnosticeerd werden tijdens een tweede re-stagerende CT scan, raadden we in dit onderzoek secundaire profylaxe aan tijdens neoadjuvante CRT bij patiënten met een belaste voorgeschiedenis. Deze aanbeveling werd vooral gebaseerd op een richtlijn uit 2007 van de American Society of Clinical Oncology[11]. Prospectieve onderzoeken zijn nodig om het gebruik en de veiligheid van profylactische therapie gedurende neoadjuvante CRT te evalueren.

Preoperatieve trombo-embolische processen kunnen, behalve het risico op een medische noodsituatie, ook invloed hebben op het postoperatieve beloop, aangezien anesthesisten terughoudend zijn om epidurale analgesie toe te passen onder bepaalde vormen van antistolling. Postoperatieve pijnstilling is van groot belang na een slokdarmresectie, omdat postoperatieve pijn gepaard kan gaan met een verminderde longfunctie, pijn bij hoesten, en een afnemende mobilisatie. Een goed werkende epidurale pijnstilling is geassocieerd met een verminderd risico op pulmonale complicaties[12]. Adequate trombo-embolische preventie is dus noodzakelijk om te voorkomen dat er een ander beleid dan epidurale analgesie wordt gevoerd. We konden echter geen verschil aantonen in het postoperatieve beloop bij patiënten met een preoperatief trombo-embolische proces.

Chemoradiotherapie voorafgaand aan een slokdarmresectie wordt verondersteld gepaard te gaan met een verhoogd risico op cardiopulmonale toxiciteit[13-15]. In **Hoofdstuk 5** hebben we het effect van neoadjuvante CRT op postoperatieve morbiditeit en mortaliteit in een gematchte groep na een slokdarmresectie geëvalueerd. Na multivariate analyse bleek neoadjuvante CRT significant geassocieerd met een verhoogd risico op de ontwikkeling van longontstekingen en hartritmestoornissen. Het totaal aantal complicaties was vergelijkbaar in beide groepen, in overeenstemming met het CROSS onderzoek[1]. De afgelopen jaren zijn tegenstrijdige resultaten gerapporteerd over de invloed van neoadjuvante CRT op postoperatieve morbiditeit en mortaliteit. De stralingsdosis op cardiopulmonale organen tijdens neoadjuvante CRT is echter substantieel. Er zijn onderzoeken die een correlatie tussen een lagere stralingsdosis en een vermindering van de pulmonale belasting laten zien[13]. Bovendien zou bestraling van het pericard leiden tot een verhoogd risico op pericardvocht, zich mogelijk uitend in postoperatieve cardiale complicaties[16]. Vervolgonderzoek zou zich dan ook moeten richten op bestralingsmethoden, die leiden tot minder schadelijke bijwerking van de straling op deze organen, zonder afbreuk te doen aan de gunstige effecten van CRT. Veel belovende stralingstechnieken zoals protonentherapie, kunnen cardiopulmonale toxiciteit verminderen.

Ziekenhuis volume wordt geassocieerd met verbeterde korte en lange termijn uitkomsten in patiënten met een slokdarmcarcinoom[17]. In een verslag (niet opgenomen in dit proefschrift) hebben we verondersteld dat het aantal uitgevoerde operaties door een chirurg in een hoog-volume ziekenhuis een onafhankelijke prognostische factor is voor de postoperatieve uitkomst na een slokdarmresectie. In dit verslag hebben we twee hoog-volume ziekenhuizen in Nederland geïncludeerd en na multivariate analyses, bleek het aantal uitgevoerde operaties door een chirurg de enige onafhankelijke prognostische factor te zijn voor een naadlekkage. Ons doel is echter om een groot deel van de noordelijk gelegen centra in Nederland te includeren, vervolg onderzoek zal hier dan ook op gericht zijn.

Het effect van een slokdarmresectie op vroege postoperatieve labwaarden en de associatie met postoperatieve morbiditeit en mortaliteit werd geëvalueerd in **Hoofdstuk 6**. Een groep van 210 opeenvolgende slokdarmpatiënten onderging een radicale transthoracale resectie. Standaard afgenomen labwaarden werden op drie verschillende tijdstippen geincludeerd met maximum tot 48 uur na de operatie. Multivariate analyses en ROC analyse toonden prognostische waarde voor lactaat dehydrogenase (LDH), creatinine en C-reactief proteïne (CRP) voor het ontstaan van infectieuze complicaties na een slokdarmresectie. Ernstige complicaties integreren met meerdere pathofysiologische mechanismen, die zich uiten middels verschillende afwijkende labwaarden. Dit bevestigt het niet-specifieke karakter van deze waarden en de daaraan gerelateerde lastige interpretatie. In dit onderzoek attenderen we clinici er op zich bewust te zijn van een mogelijk gecompliceerd postoperatieve beloop en een zo nodig vroege interventie indien deze waarden afwijkend blijken te zijn. Verder onderzoek moet gericht zijn op meer specifieke markers om postoperatieve complicaties in een vroeg stadium te identificeren. Bovendien zijn de pathofysiologische mechanismen die leiden tot een gecompliceerd postoperatief beloop nog steeds niet goed duidelijk. Een verbeterde kennis zou kunnen leiden tot vroegtijdige interventies.

In **Hoofdstuk 7** hebben we negen cytokines geëvalueerd met verschillende (patho) fysiologische mechanismen om meer inzicht te verschaffen in de immunologische reactie gedurende verschillende fasen in de multimodale behandeling van slokdarmpatiënten. In deze hypothese genererende studie hebben we 35 patiënten geïncludeerd. Om de prognostische waarde te bepalen van deze cytokines met betrekking tot de pathologische respons na CRT en de complicaties veroorzaakt door CRT of de daaropvolgende operatie, hebben we multivariate analyses uitgevoerd. Concentraties van intestinal fatty acid binding protein (I-FABP) namen na neoadjuvante CRT aanzienlijk toe, duidend op aan de behandeling gerelateerde toxische gastrointestinale beschadiging, aangezien I-FABP vrijkomt bij een beschadigde integriteit van mucosale cellen[18]. Na chirurgie namen de concentraties I-FABP juist weer sterk af. Hoge concentraties van platelet activating factor (PAF) voor en na neoadjuvante CRT waren gecorreleerd aan pathologische respons. Mogelijk is dit effect gerelateerd aan toegenomen chemotherapie-geïnduceerde effecten van PAF door activering van immunologische pathways[19]. Bovendien komt PAF vrij bij de apoptose van tumor cellen en tijdens oxidatieve stress en zowel radiotherapie als chemotherapie zijn krachtige oxidatieve stressoren[20]. Ten slotte bleek angiopoietin 1 (Ang-1) een prognostische marker voor postoperatieve complicaties gedurende verschillende fasen in de multimodale behandeling. Ang-1 is betrokken in het handhaven van de cellulaire integriteit en endotheliale barrière van vasculaire cellen[21]. Een verlaagde Ang-1 concentratie perioperatief, gerelateerd aan een verhoogde ontstekingsreactie, kan leiden tot verhoogde vasculaire permeabiliteit[22]. Verder onderzoek zou gericht moeten zijn op vermindering van de afgifte van pro-inflammatoire cytokines tijdens de chirurgische procedure. Hoog frequente jet ventilatie (HFJV) kan wellicht een bijdrage leveren aan een vermindering van deze respons. Deze ventilatietechniek voorkomt dat patiënten shunten over de niet-geventileerde long en gaat tevens gepaard met lage teugvolumes. Bovendien is aangetoond dat HFJV een veilige ventilatietechniek is tijdens een slokdarmresectie[23]. Bovenstaande hypothesen zijn gebaseerd op een relatief kleine groep patiënten, grote prospectieve studies zijn dan ook nodig om gegenereerde hypothesen te bevestigen.

In conclusie, met dit proefschrift hebben we beoogd meer inzicht te geven in de mogelijke risicofactoren die betrokken zijn in de relatieve hoge perioperatieve morbiditeit en mortaliteit bij in opzet curatieve behandeling van patiënten met een slokdarmcarcinoom. Een curatieve behandeling, bestaande uit een slokdarmresectie gecombineerd met neoadjuvante CRT, zal bij elke medisch fitte en op oncologische basis geselecteerde patiënt overwogen worden. De uitkomsten van dit proefschrift zullen er toe leiden dat clinici zich meer bewust zijn van welke behandeling-, patiënt,- en tumor-gebonden factoren betrokken zijn bij een mogelijk gecompliceerd beloop. Individualiseren van het behandelprotocol blijft een belangrijke doelstelling om de kwaliteit van leven en het postoperatieve resultaat te verbeteren.

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Curriculum Vitae

Dirk Bosch werd geboren op 24 juli 1983, te Emmerich (Duitsland). Hij groeide op in een warm gezin als middelste zoon van Jaap en Yvonne en als broer van Eric en Marc. In 1993 verhuisde het gezin naar Nederland, alwaar zij in Diepenveen kwamen te wonen. In 2002 behaalde Dirk zijn VWO diploma met het profiel Economie & Maatschappij. Na zijn eindexamen ging Dirk rechten studeren aan de Rijksuniversiteit Groningen. In dit jaar kwam hij tot de ontdekking dat dit niet de juiste studie voor hem was, waarna hij het roer radicaal omgooide. In een korte tijd behaalde Dirk alsnog het beoogde VWO diploma Natuur & Gezondheid aan het Luzac College te Arnhem. In 2005 startte Dirk met de studie geneeskunde, waar hij volledig op zijn plek bleek te zijn.

Zijn affiniteit met wetenschappelijk onderzoek kwam al vroeg naar voren. Zijn aandacht en interesse ging hierbij uit naar de behandeling van patiënten met een slokdarmcarcinoom. In zijn derde studiejaar startte hij een proefproject vanuit de Junior Scientific Masterclass (JSM) bij de afdeling Chirurgische Oncologie. Daarna volgde op dezelfde afdeling een wetenschappelijke stage en zo werd de basis gelegd voor een MD/PhD traject. In 2010 startte hij onder leiding van prof. dr. J.Th.M. Plukker (Chirurgische Oncologie) en prof. dr. M.M.R.F. Struys (Anesthesiologie) met zijn MD/PhD traject naar perioperatieve risicofactoren voor postoperatieve complicaties in patiënten met een slokdarmcarcinoom.

In 2011 behaalde Dirk zijn artsenbul en ging hij als arts-assistent met veel toewijding aan het werk op de Chirurgische Intensive Care in het UMCG. Daar kon hij zijn kennis en vaardigheden verder uitbreiden en bleek hij interesse te hebben in hemodynamische en pulmonale problematiek. Sinds januari 2014 is Dirk in opleiding tot Anesthesioloog in het UMCG.

In zijn vrije tijd mag hij graag zeilen of (zeil)bootjes opknappen, echter sinds hij de trotse papa is van Hidde, brengt hij vooral veel tijd door met zijn gezin.