Perioperative management of esophageal cancer

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General introduction

Based on ‘Stage-directed individualized therapy in esophageal cancer’

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ESOPHAGEAL CANCER

Esophageal cancer is the ninth most common cancer and the sixth most common cause of cancer-related death worldwide, with an estimated 442 000 new cases and 440 000 deaths annually[1]. The two main histological subtypes of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma. Globally, esophageal squamous cell carcinoma is the predominant histologic type, accounting for approximately 90% of esophageal cancer cases in high-risk regions of central Asia and in eastern and southern Africa[2,3]. However, in the last two decades there has been a dramatic increase in the incidence of esophageal adenocarcinoma in Western populations (5-10% increase each year), such that it has become the predominant subtype of esophageal cancer in Europe and North-America[4]. This ominous development is likely related to the rising prevalence of obesity – linked to an increased tendency for gastro-esophageal reflux disease – which are both proven risk factors for esophageal adenocarcinoma[5]. Although treatment effectiveness has improved overall 5-year survival of patients with esophageal cancer from less than 5% in the 1960s to approximately 20% in the past decade, survival rates for esophageal cancer remain poor[6,7].

Historically surgical resection of the esophagus (esophagectomy) combined with a resection of the surrounding lymph nodes (lymphadenectomy) has been the cornerstone of treatment with curative intent for patients with early and locally advanced esophageal cancer. The relatively poor overall survival rate achieved with surgery alone evoked a search for novel treatment strategies during the last decades to improve survival[8]. Because of the subsequent advances in staging and treatment techniques, patients with esophageal cancer can now be cured by various treatment strategies which requires a multidisciplinary approach. Neoadjuvant therapy with chemotherapy or chemoradiotherapy has supplemented surgery and is now a generally recommended treatment strategy for patients with locally advanced esophageal cancer[9,10]. While the benefit of an organized multidisciplinary approach for these patients in terms of survival is well-recognized, the optimal treatment algorithm to achieve most optimal outcomes remains an area of significant controversy.

The currently available multimodality treatment strategies have been associated with an increase in morbidity resulting in a persistent reduction in health related quality of life, and yet still a relatively poor prognosis[11]. Furthermore, while the “average patient” may respond optimally to the current available treatment, some patients may experience little to no treatment benefit at the costs of a decrease in quality of life. One of the primary reasons why not all patients respond to – or some suffer from – the currently available treatment regimens can be attributed to high inter-patient variability in response to such treatment. Factors that

contribute to this variability include etiology, histopathology, molecular underpinnings, extent of disease, underlying physical conditions and social circumstances[12,13]. By acknowledging that there is no such thing as a typical esophageal cancer patient, it is unlikely that there is a single course of treatment that will meet the need of every patient.

Therefore optimization of patient selection and improvement in the use of existing therapeutic tools are essential to minimize treatment related morbidity and ensure maximal benefit of treatment. To this regard the aim of the current thesis was to make improvements in staging (**Part 1**), treatment response prediction (**Part 2**), and in postoperative complication management (**Part 3**) of patients with esophageal cancer.

STAGING

Clinical staging

One of the key points for the treatment of esophageal cancer is accurate staging. This allows for prediction of prognosis, and direct treatment strategies to patients who are most likely to benefit from such treatment. In general, staging of esophageal tumors consists of upper-gastrointestinal endoscopy with biopsy to verify diagnosis, endoscopic ultrasonography to obtain information on the depth of tumor invasion and loco-regional nodal disease, and positron emission tomography with integrated computed tomography (PET/CT) to evaluate loco-regional spread and distant metastases[14]. Tumor stages are currently classified according to the 7th edition of the International Union Against Cancer tumor-node-metastasis (TNM) classification[15].

In some national guidelines the addition of cervical ultrasonography to conventional staging modalities is recommended in order to assess the involvement of cervical lymph node metastases[16,17]. However, integrated PET/CT – which was included as standard staging modality during the last decade – has shown to be superior to conventional imaging modalities in the preoperative staging of esophageal cancer[18,19]. Therefore, the additional diagnostic value of cervical ultrasonography to standard PET/CT for the detection of the cervical lymph nodes may be limited. As such, it would be of interest to investigate the additional value of cervical ultrasonography over PET/CT in current clinical practice (Chapter 2).

Currently there is disagreement between national guidelines whether all patients should be restaged with PET/CT after neoadjuvant chemoradiotherapy[17,20,21]. Detection of metastasis in this phase of treatment would probably prevent a futile attempt at curative esophagectomy. Although several small studies have assessed the role of PET/CT for pre-surgical restaging,

the diagnostic accuracy of this modality for the detection of interval metastasis remains unclear. Furthermore, identification of patient's individual risk of metastases after neoadjuvant chemoradiotherapy would enable a more individualized application of PET/CT restaging and reduce the number of unbeneficial diagnostic tests (Chapter 3).

Although a multimodality treatment approach is increasingly recommended for patients with locally advanced esophageal cancer, controversy still exists regarding the optimal treatment strategy for patients with clinical T2N0 tumors. As T2N0 disease represents an anticipated early stage disease, a surgery alone approach may be regarded as appropriate treatment for these tumors[22,23]. On the other hand, due to the limitations of current clinical staging several studies recommend a multimodality treatment approach for these patients[24,25]. Because the available studies on this topic are equivocal, it would be of interest to assess the current status of clinical staging and determine whether the addition of neoadjuvant chemoradiotherapy to surgery is associated with improved outcomes in a large population-based cohort of patients with clinical T2N0 esophageal tumors (Chapter 4).

Detection of disease recurrence

The relatively poor survival of esophageal cancer patients is partially attributable to the high incidence (49-85%) of disease recurrence after finishing therapy[26]. Imaging with PET/CT has shown to possess the ability to detect recurrent esophageal cancer in a pre-symptomatic phase after treatment[27]. However, a clear overview of the diagnostic value of PET/CT in this setting is lacking (Chapter 5). The subsequent challenge for the present clinical practice is the timing and frequency of surveillance PET/CT scans after treatment. Presently, half of the patients who develop recurrent disease are detected by the onset of symptoms between apparently normal surveillance scans[28]. As such there is need for accurate prediction of disease recurrence after esophageal cancer treatment (Chapter 6 and 7), as this may guide risk-stratified surveillance strategies and prompt earlier initiation of interventions to improve survival.

TREATMENT RESPONSE PREDICTION

Through tumor downsizing and downstaging, the use of neoadjuvant chemoradiotherapy improves locoregional control and overall survival rates compared to surgery alone[8,9]. Many studies have reported that the degree of tumor regression in response to chemoradiotherapy is directly related to long-term survival, with pathologic complete responders having the most favorable long-term prognosis[29,30]. Accurate prediction of pathologic complete responders before surgery would enable investigators to study the feasibility and outcome of an organ-preserving strategy (i.e. omission of surgery and close clinical follow-up) after

chemoradiotherapy[31]. On the other hand, patients with a poor response may benefit less or not at all from chemoradiotherapy but are exposed to its toxicity. A reliable identification of poor responders early during treatment would enable investigators to study the feasibility and outcome of early modification or discontinuation of neoadjuvant chemoradiotherapy. Seeking effective tools for treatment response assessment in this setting is an important focus of research with the aim to tailor treatment to the individual patient.

Various opportunities for improvement in treatment response prediction are currently under investigation. Metabolic and functional imaging modalities such as PET/CT, diffusion-weighted magnetic resonance imaging (DW-MRI), and dynamic contrast-enhanced MRI (DCE-MRI) may be promising to this regard. These modalities enable biological and microstructural characterization of tumors and visualization of treatment-induced changes before volumetric changes become apparent. Indeed, previous studies have shown that PET/CT, DW-MRI and DCE-MRI appear to provide valuable information regarding the assessment of response to treatment in esophageal cancer[32–34]. However, the discriminative ability of these modalities in a standalone fashion have so far been insufficient to guide clinical decision making[32–34]. Therefore, it is of interest to assess whether these three imaging markers provide complementary information in a multimodality setting to ultimately provide sufficient predictive ability to accurately predict treatment response (Chapters 8 and 9). At the same time, however, little is known about the perceived burden of all these tests by patients. In order to improve patient-friendliness of restaging procedures, it is necessary to evaluate the burden of these diagnostic procedures from the perspective of the patient (Chapter 10).

POSTOPERATIVE COMPLICATION MANAGEMENT

Esophagectomy has an important role in the treatment of esophageal cancer, but is accompanied by a high operative risk[35]. Reported overall frequency rates of complications after esophagectomy range between 40% and 60%, with pulmonary and anastomotic complications being the most common complications[36,37]. These postoperative complications have a significant effect on morbidity, length of hospital stay and mortality[38]. Although advances in surgical techniques and perioperative care have reduced the frequency of complications over the years, postoperative morbidity remains high[39]. Therefore, further quality improvement efforts in esophageal surgery are required. In order to develop and prioritize quality improvement initiatives, complications that have the greatest overall impact on costs (Chapter 11) and patient outcomes (Chapter 12) after esophagectomy have first to be identified.

Subsequently, accurate risk assessment of these complications prior to surgery could aid in early recognition of these complications, in the selection of patients who may benefit from preoperative preventative strategies, and in choosing the extent of the operation. Currently, accurate prediction of postoperative complications based on standard patient or treatment-related characteristics remains difficult. Recently atherosclerotic calcification of the locoregional arteries supplying the gastric tube was identified as independent risk factor for anastomotic leakage after esophagectomy[40]. In order to use this new risk factor in clinical practice it is necessary to assess its generalizability in an independent cohort of patients (Chapter 13). In the pursuance of adequate preoperative preventive strategies for postoperative complications, it is of interest to assess whether the association between atherosclerotic calcification and anastomotic leakage applies to local vascular disease (with accompanied local flow limitations) only, or to generalized vascular disease as well (Chapter 14). Other potential preoperative risk factors that may hold important prognostic value for the prediction of postoperative complication include intraoperative and postoperative vital parameters (Chapter 15).

In patients with locally advanced esophageal cancer both neoadjuvant chemotherapy and chemoradiotherapy have demonstrated a survival advantage over surgery alone[8,9,41]. However, after the introduction of neoadjuvant chemoradiotherapy in clinical practice, several hospitals reported a vast increase in their postoperative complication rate[42,43]. Therefore, it is of interest to compare toxicity and postoperative complications between perioperative chemotherapy and neoadjuvant chemoradiotherapy (Chapter 16). Furthermore, it was hypothesized that radiation exposure to the gastric fundus may impair anastomotic healing, as this part of the stomach is used for constructing the esophagogastric anastomosis[44]. Before efforts are made to spare the gastric fundus in radiation treatment planning, the potential association between radiation dose to the gastric fundus and anastomotic leakage should be further explored (Chapter 17).

In esophageal surgery controversy remains about certain operative techniques, as they may be associated with postoperative complications. In this regard, the optimal anatomical location of the esophagogastric anastomosis (i.e. intrathoracic versus cervical) after esophagectomy is unclear. Several studies reported increased leak rates in patients with a cervical anastomosis[45,46], while other studies did not[47,48]. Since the scientific evidence for an association between the location of the anastomosis and risk of anastomotic leakage remains equivocal, it is of great interest to explore this association in a nationwide setting (Chapter 18).

In case anastomotic leakage after esophagectomy occurs, early detection is crucial since delayed treatment is associated with significant morbidity and mortality[49]. Currently, CT scanning is commonly performed for diagnosis of leakage, since it is non-invasive and safe to use in critically ill patients[50]. However, objective criteria to detect anastomotic leakage on CT have not been clearly defined. Therefore, it is of interest to identify reliable CT findings that can be used to diagnose anastomotic leakage (Chapter 19).

RESEARCH OBJECTIVE PER CHAPTER

Part 1. Staging

Chapter 2 To determine the additional value of cervical ultrasonography over PET/CT for diagnosing cervical lymph node metastases in patients with newly diagnosed esophageal cancer

Chapter 3 To determine the diagnostic performance of PET/CT for the detection of interval metastasis after neoadjuvant chemoradiotherapy and to identify predictors of interval metastases

Chapter 4 To evaluate current clinical staging and determine whether the addition of neoadjuvant chemoradiotherapy to surgery is associated with improved survival in patients with clinical T2N0M0 esophageal cancer

Chapter 5 To review the diagnostic performance of PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent

Chapter 6 To develop a preoperative prediction model for early recurrence after neoadjuvant chemoradiotherapy and surgery for esophageal adenocarcinoma

Chapter 7 To externally validate a postoperative prediction model for survival after neoadjuvant chemoradiotherapy and surgery for esophageal cancer

Part 2. Treatment response prediction

Chapter 8 To evaluate whether the apparent diffusion coefficient acquired by DW-MRI and the standardized uptake value acquired by PET/CT are correlated or independent functional imaging markers

Chapter 9 To explore the distinct and combined value of DCE-MRI and DW-MRI during and after neoadjuvant chemoradiotherapy to predict pathologic response

Chapter 10 To evaluate the experienced burden associated with repeated PET/CT and MRI examinations during neoadjuvant chemoradiotherapy from the perspective of the patient

Part 3. Postoperative complication management

Chapter 11 To determine the economic burden of postoperative complications after esophagectomy

Chapter 12 To identify which postoperative complications after esophagectomy have the greatest impact on clinical outcomes

Chapter 13 To evaluate the relationship between atherosclerotic calcification of the arteries supplying the gastric tube and anastomotic leakage after Ivor-Lewis esophagectomy

Chapter 14 To evaluate the relationship between atherosclerotic calcification of the entire cardiovascular system with the occurrence of anastomotic leakage after Mckeown esophagectomy

Chapter 15 To assess the relationship of intraoperative and postoperative vital parameters with anastomotic leakage and pneumonia after esophagectomy

Chapter 16 To compare toxicity, postoperative complications and survival after perioperative chemotherapy and neoadjuvant chemoradiotherapy followed by surgery for patients with esophageal adenocarcinoma

Chapter 17 To determine the influence of radiation dose to the gastric fundus on the risk of anastomotic leakage in patients undergoing neoadjuvant chemoradiotherapy followed by esophagectomy

Chapter 18 To compare clinical outcome after esophagectomy in patients with an intrathoracic or cervical anastomosis, and to identify predictors of anastomotic leakage

Chapter 19 To develop a CT-based prediction score for anastomotic leakage after esophagectomy and compare it to subjective CT interpretation

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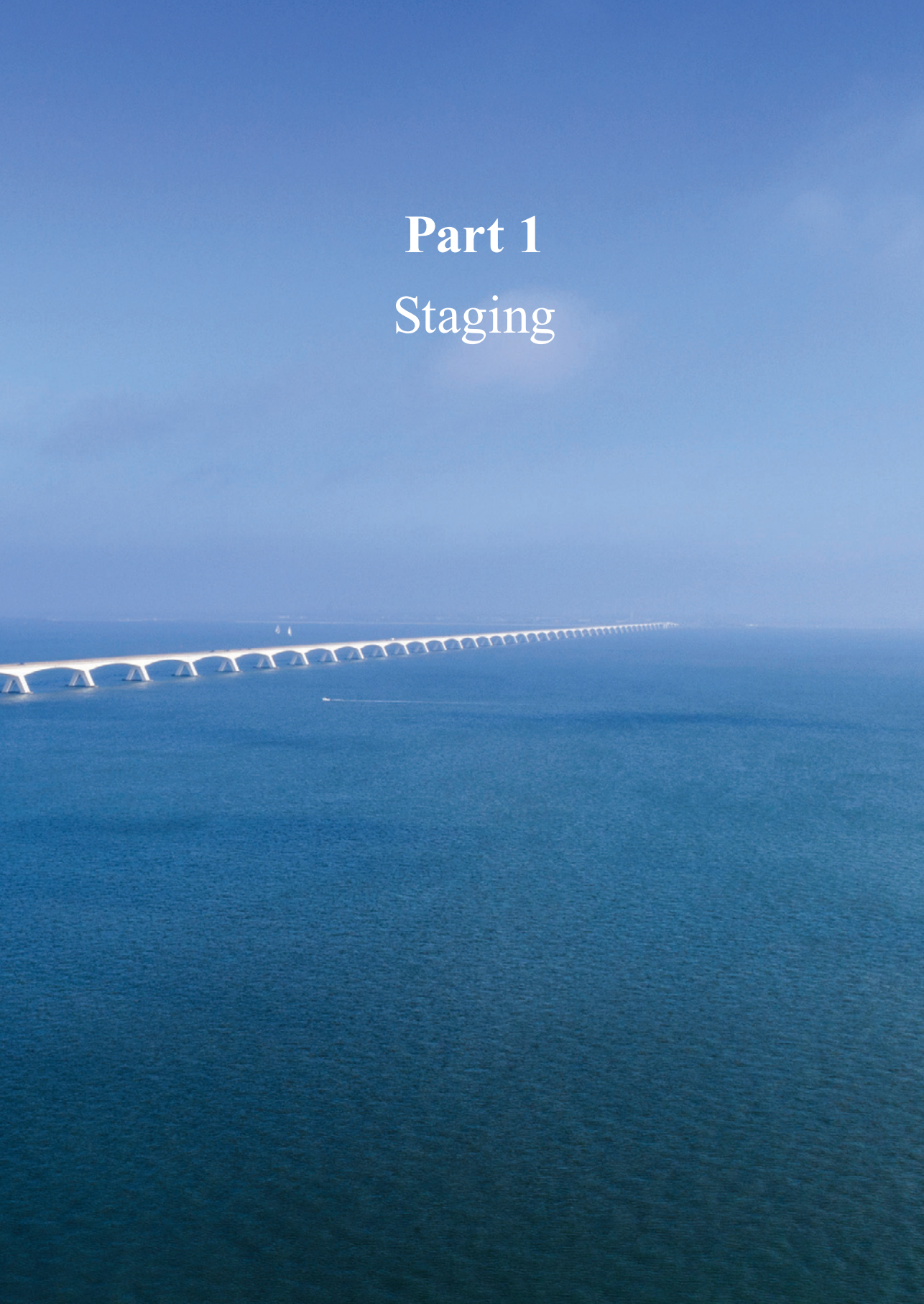

Part 1

Staging

2

Cervical ultrasonography has no additional value over a negative PET/CT for diagnosing cervical lymph node metastases in patients with esophageal cancer

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ABSTRACT

Objective

To investigate the additional value of cervical ultrasonography over ^{18}F-FDG PET/CT for diagnosing cervical lymph node metastases in patients with newly diagnosed esophageal cancer.

Methods

Between January 2013 and January 2016, 163 patients with newly diagnosed esophageal cancer underwent both cervical ultrasonography and ^{18}F-FDG PET/CT at a tertiary referral center in the Netherlands. Retrospective clinical data analysis was performed to assess the diagnostic value of cervical ultrasonography and ^{18}F-FDG PET/CT for the detection of cervical lymph node metastases. Fine needle aspiration or clinical follow-up was used as reference standard.

Results

The overall incidence of patients with cervical lymph node metastases was 14%. The sensitivity of ^{18}F-FDG PET/CT to detect cervical lymph node metastases was 82% (95%CI: 59%-94%) and specificity was 91% (95%CI: 85%-95%). The sensitivity and specificity of cervical ultrasonography were 73% (95%CI: 50%-88%) and 84% (95%CI: 77%-90%), respectively. In patients with a negative ^{18}F-FDG PET/CT, 12 of 133 (9%) patients had suspicious nodes on cervical ultrasonography. In all these 12 patients the nodes were confirmed benign.

Conclusion

Cervical ultrasonography has no additional diagnostic value to a negative integrated ^{18}F-FDG PET/CT for the detection of cervical lymph node metastases in patients with newly diagnosed esophageal cancer.

INTRODUCTION

Esophageal cancer is the eighth most prevalent cancer, and the sixth most common cause of cancer-related death worldwide[1]. Surgical resection of the esophagus with en-bloc lymphadenectomy remains the cornerstone treatment with curative intent for patients with non-metastatic esophageal cancer[2, 3]. Currently, a multimodal treatment approach is increasingly applied since many studies have shown a survival benefit of neoadjuvant chemo(radio)therapy over surgery alone for patients with resectable esophageal cancer[4-6].

Accurate staging of esophageal cancer is essential to select patients that are eligible for treatment with curative intent, and to identify patients with distant metastases to prevent a non-curative surgical procedure. Currently recommended staging techniques include endoscopic ultrasound (EUS) with fine needle aspiration (FNA), ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) with integrated diagnostic computed tomography (CT) of the neck, chest and abdomen, and cervical ultrasonography with FNA[7]. In some guidelines the use of cervical ultrasonography is recommended since this is considered an effective and accurate approach to assess cervical lymph node involvement[7, 8]. However, the introduction of integrated ^{18}F-FDG PET/CT scanning has improved the accuracy of cancer staging by providing both anatomical and metabolic information[9]. Therefore, the additional role of cervical ultrasonography for the detection of cervical lymph node metastases in the current era of routine diagnostic ^{18}F-FDG PET/CT imaging may be limited.

Accordingly, the aim of this study was to investigate the additional value of cervical ultrasonography over ^{18}F-FDG PET/CT for diagnosing cervical lymph node metastases in patients with newly diagnosed esophageal cancer.

METHODS

Institutional review board approval was obtained, and requirement for written informed consent was waived for this cohort study. In this study all patients referred to the University Medical Center Utrecht with newly diagnosed esophageal cancer, between January 2013 and January 2016, were identified from a prospectively collected database. Within this cohort, patients who were evaluated with both integrated ^{18}F-FDG PET/CT and cervical ultrasonography were included. The two investigations of interest were performed in random order. Cervical lymph nodes suspicious for metastasis based on cervical ultrasonography and/or ^{18}F-FDG PET/CT underwent FNA and cytopathological examination. Clinical follow-up data from all patients were collected to identify cervical metastases that were potentially undetected during clinical staging. Therewith, the composite reference standard of the current study included

either positive cytopathology of the aspirated material from a suspicious cervical lymph node during initial staging, or the occurrence of a new cervical lymph node metastasis that were detected within 12 months of clinical follow-up after initial staging and proven malignant with cytology. Cervical lymph node metastases were group into levels corresponding with upper, middle, and lower jugular nodes (levels II, III, IV, respectively), and posterior triangle nodes (level V). After completion of staging all patients with a clinical stage T1N1-3 or T2-4aN0-3, with no evidence of distant or pathologically confirmed cervical metastases, were scheduled for esophagectomy with en-bloc two-field lymphadenectomy.

Cervical ultrasonography with FNA

Ultrasonography of the cervical and supraclavicular region was performed by experienced radiologists, using a 12.5 to 17.5 MHz linear array transducer (Philips Medical Systems, Best, The Netherlands). Cervical lymph nodes with a short axis diameter of ≥5mm (≥7mm for high jugular / level II nodes), or <5mm nodes with a prominent appearance (round shape, loss of fatty hilum, [focal] low echogenicity, or an eccentric mass), and grouped nodes with a short axis diameter of ≥3mm were considered suspicious for metastasis and cytologically examined after FNA.

Integrated ^{18}F-fluorodeoxyglucose PET/CT

Patients had to stay sober for at least six hours before injection of ^{18}F-FDG, and blood glucose levels were measured to check for potential hyperglycemia. The administered activity of intravenously administered ^{18}F-FDG was 2.0 MBq/kg. Approximately 60 minutes after administration of ^{18}F-FDG, PET and CT imaging were performed from neck to abdomen in all patients using a PET/CT system (mCT, Siemens, Erlangen, Germany). Before PET acquisition a diagnostic quality Iodine contrast-enhanced CT was performed using the following settings: 120 kV, 20 mA, 0.5 s tube rotation time, pitch of 1.0, and 3.0 mm slice width. PET was performed using 3-dimensional acquisition, an axial field of view of 216 mm, and a scanning time of 3 minutes/bed position. ^{18}F-FDG PET/CT data were reconstructed using iterative ordered-subsets expectation maximization for 21 subsets and 4 iterations (Gaussian filter). All ^{18}F-FDG PET/CT images were visually interpreted by experienced nuclear medicine physicians. Cervical nodes were considered suspected on PET/CT if they had increased non-physiological ^{18}F-FDG uptake based on visual interpretation without size constraints. Additional FNA was performed in case of suspicious lymph nodes.

Follow-up

The duration of clinical follow-up was calculated from the date of last diagnostic work-up (^{18}F-FDG PET/CT or cervical ultrasonography) until identification of cervical lymph node metastases, last visit at the outpatient clinic or death. The median follow-up of all eligible patients included in this study was 11 months (interquartile range: 6 to 15 months). The time of follow-up of patients without lymph node metastases that were still alive during follow up was at least 12 months.

Statistical analysis

Sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG PET/CT and cervical ultrasonography for the detection of cervical lymph node metastases were calculated. Sensitivity and specificity was compared using McNemar's test, and PVV and NPV using the Chi-square test, between ^{18}F-FDG PET/CT and cervical ultrasonography, respectively. The additional value of cervical ultrasonography to ^{18}F-FDG PET/CT was determined by calculating the proportion of patients with a positive cervical ultrasonography that was confirmed malignant, in the group of patients with a negative ^{18}F-FDG PET/CT scan. Differences in diagnostic performance were explored using sensitivity analyses including distant cervical lymph node metastasis (level II), regional cervical lymph node metastasis (level III,IV,V), and squamous cell tumors.

RESULTS

Between January 2013 and January 2016 252 patients with newly diagnosed esophageal cancer were referred to our tertiary referral center. Of these patients, 89 were excluded of this study because ^{18}F-FDG PET/CT (n=45) or cervical ultrasonography (n=36) was not performed, or both cervical ultrasonography and ^{18}F-FDG PET/CT were not performed (n=8). The main reasons to refrain from cervical ultrasonography of the neck was previous imaging showing distant metastases. In case a ^{18}F-FDG PET/CT was not performed, this was mainly due to the gradual introduction of this imaging modality for this indication in our hospital in the first year of the study period. These patients underwent a CT scan only. A total of 163 patients underwent both cervical ultrasonography and ^{18}F-FDG PET/CT imaging, and were included in the current analysis. Figure 1 shows the flowchart of patient selection, and Table 1 demonstrates the patient and treatment-related characteristics. The overall incidence of patients with cervical lymph node metastases was 14%. Of the 22 cervical lymph node metastasis, 2 (9%), 4 (18%), 15 (68%) and 1 (5%) were located in levels II, III, IV and V, respectively.

Cervical ultrasonography and ^{18}F-FDG PET/CT non-suspected nodes

Cervical ultrasonography and ^{18}F-FDG PET/CT were both negative for cervical lymph node metastases in 121 out of 163 (74%) of the patients, and therefore no FNA was performed. During clinical follow-up 4 of these 121 initially non-suspected patients developed cervical lymph node metastases, which were confirmed malignant after 6, 7, 7 and 12 months, respectively.

Cervical ultrasonography and ^{18}F-FDG PET/CT suspected nodes

Cervical ultrasonography and ^{18}F-FDG PET/CT were both suspected for presence of cervical lymph node metastases in 26 out of 163 (16%) patients. In 24 out of 26 of these patients FNA was performed, of whom 16 were cytologically confirmed malignant and 8 were benign. In two patients it appeared impossible to perform FNA due to small size and inaccessibility of the lymph nodes. These patients underwent primary esophagectomy with two-field lymphadenectomy and had no signs of cervical metastases after 12 and 19 months of clinical follow-up, respectively. All false-positive nodes (18 out of 26) showed increased FDG uptake, and had a short axis diameter ranging between 5 and 10 mm.

Cervical ultrasonography suspected nodes

In 12 of 163 (7%) patients only cervical ultrasonography showed suspected cervical lymph nodes, while ^{18}F-FDG PET/CT was negative. FNA showed 10 false-positives and 2 patients had an inconclusive FNA. The patients with inconclusive FNA underwent surgery and had no signs of cervical metastases after 29 and 30 months of clinical follow-up, respectively.

^{18}F-FDG PET/CT suspected nodes

In 4 of 163 (3%) patients only ^{18}F-FDG PET/CT was suspected for cervical lymph node metastases during diagnostic work-up, while cervical ultrasonography was negative. In 2 patients the suspected nodes were cytologically confirmed malignant (n=1) or benign (n=1) after FNA. In the other 2 patients FNA was not performed. In one of these patients a CT scan showed enlargement of the cervical lymph node 3 months after initial diagnostic work-up, which was therefore considered malignant. This patient underwent definitive chemoradiotherapy and died a few months after diagnosis of the cervical metastasis. The other patient underwent surgery and showed no cervical metastases during the first 18 months of clinical follow-up.

Diagnostic performance

The comparison of diagnostic performance between, ^{18}F-FDG PET/CT and cervical ultrasonography to detect malignant lymph nodes and subsequent subgroup analysis are summarized in Table 2. The sensitivity and specificity of ^{18}F-FDG PET/CT was 82% (95% CI: 59-94%); and 91% (95% CI: 85-95%), respectively. Positive and negative predictive values of ^{18}F-FDG PET/CT were 60% (95% CI: 41-77%) and 97% (95% CI: 23-59%), respectively. The sensitivity and specificity of cervical ultrasonography was 73% (95% CI: 50-88%), whereas the specificity was 84% (95% CI: 77-90%). Positive and negative predictive values of cervical ultrasonography were 42% (95% CI: 27-59%) and 95% (95% CI: 41-73%), respectively (Table 2). Both sensitivity and specificity were significantly higher for ^{18}F-FDG PET/CT scanning compared to cervical ultrasonography. In the various subgroup analyses, ultrasonography did not outperform ^{18}F-FDG PET/CT scanning for the detection of cervical lymph node metastasis. Overall, there was no (0% [0/133]) additional value of a cervical ultrasonography to a negative ^{18}F-FDG PET/CT scan for the detection of cervical lymph node metastases

TABLE 1. Baseline characteristics

Characteristic	n (%)
Male gender	114 (70)
Age (years)*	67.2 (±8.6)
Tumor location	
Proximal esophagus	21 (13)
Middle esophagus	45 (28)
Distal esophagus	74 (45)
GEJ/cardia	23 (14)
Histology	
Adenocarcinoma	94 (58)
Squamous cell carcinoma	66 (40)
Other	3 (2)
Clinical T-stage	
T1	16 (10)
T2	25 (15)
T3	102 (63)
T4	18 (11)
Tx	2 (1)
Clinical N-stage	
N0	28 (17)
N1	59 (36)
N2	42 (26)
N3	34 (21)

TABLE 1 (continued). Baseline characteristics

Characteristic	n (%)
Clinical M-stage	
M0	143 (88)
M1	20 (12)

GEJ = gastroesophageal junction
*Expressed as mean ± standard deviation.

TABLE 2. Comparison of diagnostic parameters of ^{18}F-FDG PET/CT and cervical ultrasonography, including subgroup analysis

	^{18}F-FDG PET/CT	Cervical ultrasonography	P-value
Overall			
SE (%) [95%CI]	18/22 (82%) [59-94]	16/22 (73%) [50-88]	0.012
SP (%) [95%CI]	129/141 (73%) [50-88]	119/141 (84%) [77-90]	0.013
PPV (%) [95%CI]	18/30 (60%) [41-77]	16/38 (42%) [27-59]	0.222
NPV (%) [95%CI]	129/133 (97%) [23-59]	119/125 (95%) [41-73]	0.675
Squamous cell carcinoma			
SE (%) [95%CI]	7/9 (78%) [40-97]	6/9 (67%) [30-92]	0.289
SP (%) [95%CI]	52/57 (91%) [81-97]	47/57 (82%) [70-91]	0.063
PPV (%) [95%CI]	7/13 (58%) [36-77]	6/16 (38%) [22-55]	0.477
NPV (%) [95%CI]	52/54 (96%) [88-99]	47/50 (94%) [86-98]	0.929
Level III,IV,V lesions			
SE (%) [95%CI]	17/20 (85%) [62-97]	15/20 (75%) [51-91]	0.008
SP (%) [95%CI]	127/135 (94%) [87-97]	118/135 (87%) [81-92]	0.012
PPV (%) [95%CI]	17/25 (68%) [51-81]	15/32 (47%) [35-60]	0.185
NPV (%) [95%CI]	127/130 (98%) [93-99]	118/122 (96%) [92-98]	0.932
Level II lesions			
SE (%) [95%CI]	2/3 (67%) [9-99]	2/3 (67%) [9-99]	1.000
SP (%) [95%CI]	119/123 (97%) [92-99]	118/123 (96%) [91-99]	1.000
PPV (%) [95%CI]	2/6 (33%) [3-64]	2/7 (29%) [11-56]	0.852
NPV (%) [95%CI]	119/120 (99%) [96-100]	118/119 (99%) [96-100]	0.995

TP = true positive. TN = true negative. FP = false positive. FN = false negative. SE = sensitivity. SP = specificity. PPV = positive predictive value. NPV = negative predictive value.

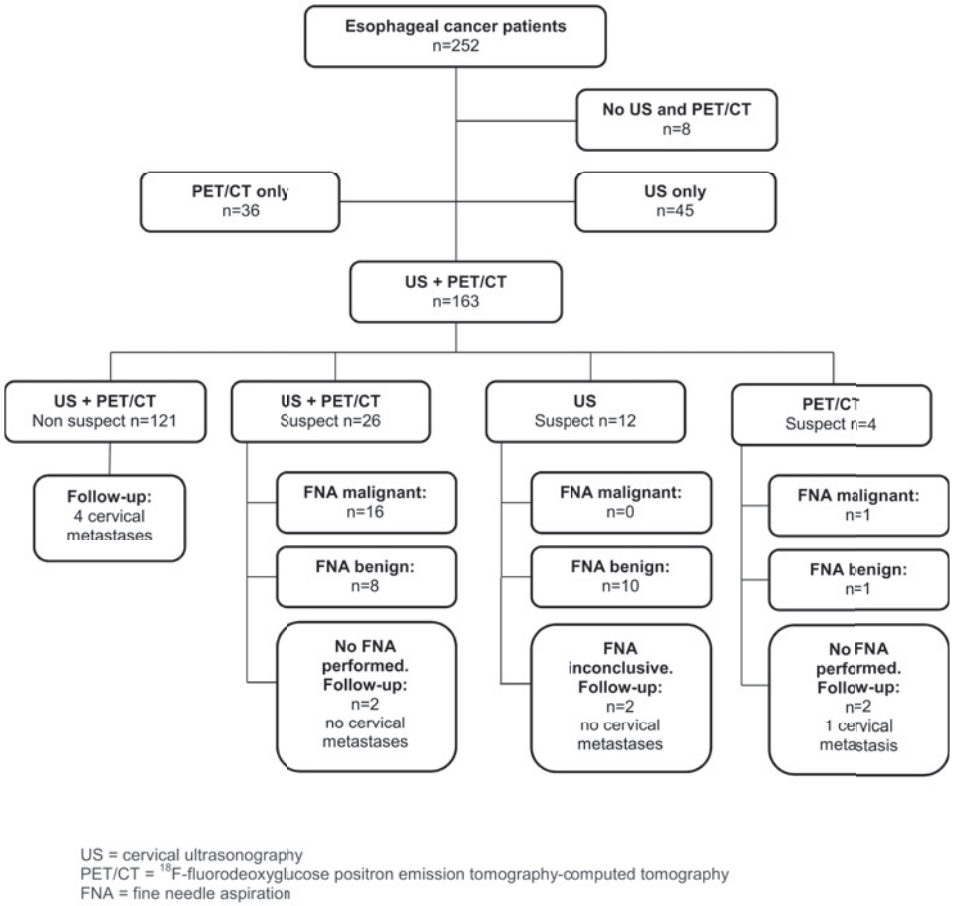

Figure 1. Flowchart of patients (n=163) with primary esophageal cancer who underwent ^{18}F-FDG PET/CT and cervical ultrasonography between January 2014 and January 2016.

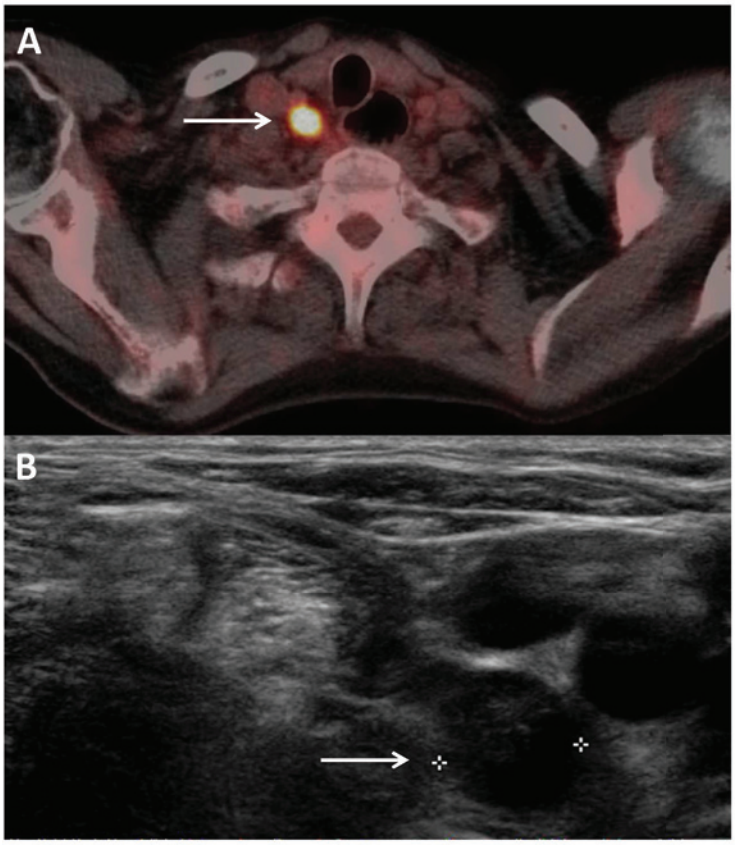

Figure 2. A. Fused axial PET/CT image demonstrating a 10 mm FDG avid cervical lymph lymphnode metastasis in station IV (right) during initial staging in a patient with a primary esophageal squamous cell tumor (arrow). **B.** Cervical ultrasonography image in the same patient, demonstrating a 10 mm cervical round-shaped lymph node metastasis in level IV (right). The cervical lymph node was confirmed malignant with FNA (arrow).

DISCUSSION

In the current cohort study the additional diagnostic value of cervical ultrasonography to ^{18}F-FDG PET/CT scanning for the detection of cervical lymph node metastases in patients with newly diagnosed esophageal cancer was evaluated. Results from the current cohort of patients demonstrated no additional value of cervical ultrasonography to integrated ^{18}F-FDG PET/CT scanning.

Several studies suggest that in case of cervical lymph node involvement an aggressive approach with radical esophagectomy combined with a three-field lymphadenectomy is justified[10]. However, in most Northern American and European countries presence of cervical lymph node metastases is still considered as systemic disease. Therefore, it is argued that survival will not increase despite removal of these lymph nodes. In that case different palliative therapies are applied for patients with cervical lymph node metastases[11, 12]. Because the presence of cervical lymph node metastases will have a major influence on both prognosis and therapeutic decisions, accurate diagnosis of cervical lymph node metastasis is crucial.

Integrated ^{18}F-FDG PET/CT scanning has significantly improved the accuracy of esophageal cancer staging, and frequently influences patient management[13]. Therefore, the use of integrated ^{18}F-FDG PET/CT is currently highly recommended in initial esophageal cancer staging[13]. Due to the improvement in esophageal cancer staging by ^{18}F-FDG PET/CT scanning it has been suggested that the additional role of cervical ultrasonography for the detection of cervical lymph node metastasis may be limited[14]. This hypothesis was confirmed in the current cohort of patients in which no additional value of cervical ultrasonography was found to integrated ^{18}F-FDG PET/CT scanning for the detection of cervical metastasis. With regard to sensitivity, specificity, PPV and NPV of both diagnostic modalities (Table 2), ^{18}F-FDG PET/CT scanning performed better on all these domains compared to cervical ultrasonography. Even though cervical ultrasonography yielded a NPV of 95%, this did not result in an additional value over ^{18}F-FDG PET/CT which yielded an even higher NPV of 97%. Also, no subgroup in which ultrasonography outperformed ^{18}F-FDG PET/CT scanning for the detection of cervical metastasis could be identified. However, suspected cervical lesions detected with ^{18}F-FDG PET/CT still require cytopathological confirmation by FNA because of possible false-positives (encountered in 12 of 163 [7%] patients in the current study).

Our results are consistent with two articles found in literature that reported no additional value of cervical ultrasonography to integrated ^{18}F-FDG PET/CT scanning (or standalone PET combined with CT) for detecting cervical lymph node metastases (n=170 and n=136, respectively)[14, 15]. One study found an additional value of 4% (3/74) of cervical ultrasonography over standalone PET and CT imaging (n=109)[16]. Methodological differences between the various studies could explain some of the discrepancies in reported added value of cervical ultrasonography. First, two studies only assessed standalone PET and CT[15, 16]. This may have led to an underestimation of the diagnostic value of PET/CT, as standalone PET and CT may result in lower diagnostic accuracies compared to integrated ^{18}F-FDG PET/CT scanning. To this regard, the only study so far that used integrated ^{18}F-FDG PET/CT scanning demonstrated

no additional value of cervical ultrasonography for the detection of cervical lymph node metastases [14]. The current study was able to confirm these results in an independent set of patients, which suggested external generalizability to other patient populations. Second, criteria for positive cervical lymph nodes on both ^{18}F-FDG PET/CT and cervical ultrasonography were heterogeneous throughout the different studies, and were often operator-dependent[14-16]. However, the results of the current study and those present in the current literature represent cervical lymph node staging in daily practice[14-16].

In the current cohort study, the incidence of cervical lymph node metastases was 14% (22/163). This rate is high compared to the other studies assessing the additional value of cervical ultrasonography, which reported incidences of cervical lymph node metastases ranging between 3% and 9%[14-16]. This difference can be explained by the fact that the current study included a relatively high number of proximal (13%) and squamous cell tumors (40%) compared to the other studies. It is well known that these type of tumors, at these locations, have a higher incidence of cervical lymph node metastases[17]. Even higher incidences of 27-31% have been described in case extensive pathological examination is performed after three-field lymph node dissection[18, 19].

Potential limitations apply to this study. First, in our cohort study the image analysts were not blinded for the results of earlier conducted investigations, which may have influenced the interpretation of the different tests. Second, cervical lymph node metastasis may have been missed by both imaging modalities, as no pathological evaluation was available for patients with a negative test. These patients were evaluated by clinical follow-up, which is a potentially less reliable reference test. To this regard, differential verification bias was of concern in the current study because different reference standards were used for the detection of cervical lymph nodes[20]. Third, the time interval (e.g. 6 or 12 months) in which positive findings at follow-up are regarded as false-negatives influences the diagnostic values of the different modalities. Changing the time interval of the current study from 12 to 6 months, for example, would have resulted in an overestimation of the reported sensitivities of both modalities. However, in the current study changing the time interval to 6 months would not have influenced the added value of cervical ultrasonography over ^{18}F-FDG PET/CT.

In conclusion, this study demonstrates that cervical ultrasonography has no additional diagnostic value over a negative ^{18}F-FDG PET/CT for the detection of cervical lymph node metastases in patients with newly diagnosed esophageal cancer. Especially since the introduction of integrated ^{18}F-FDG PET/CT systems, cervical ultrasonography during standard

diagnostic work-up of esophageal cancer patients may be considered unnecessary. Suspected cervical lesions on ^{18}F-FDG PET/CT still require cytopathological confirmation by FNA because of possible false-positive results.

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3

Prediction and diagnosis of interval metastasis after neoadjuvant chemoradiotherapy for esophageal cancer using PET/CT

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ABSTRACT

Objective

During neoadjuvant chemoradiotherapy for esophageal cancer or in the interval prior to surgery some patients develop systemic metastasis. This study aimed to evaluate the diagnostic performance of ^{18}F-FDG PET/CT for the detection of interval metastasis and to identify predictors of interval metastases in a large cohort of esophageal cancer patients.

Methods

In total 783 consecutive patients with potentially resectable esophageal cancer who underwent chemoradiotherapy and pre- and post-treatment ^{18}F-FDG PET/CT between 2006 and 2015 were analyzed from a prospectively maintained database. Diagnostic accuracy measures were calculated on a per-patient basis using histological verification or clinical follow up as reference standard. Multivariable logistic regression analysis was performed to determine pre-treatment predictors of interval metastasis. A prediction score was developed to predict the probability of interval metastasis.

Results

Of 783 patients that underwent ^{18}F-FDG PET/CT restaging, 65 (8.3%) were found to have interval metastasis and 44 (5.6%) were deemed to have false positive lesions. The resulting sensitivity and specificity was 74.7% (95% CI: 64.3-83.4%) and 93.7% (95% CI: 91.6-95.4%), respectively. Multivariable analysis revealed that tumor length, cN status, squamous cell tumor histology, and baseline SUV_{max} were associated with interval metastasis. Based on these criteria, a prediction score was developed with an optimism adjusted C-index of 0.67 that demonstrated accurate calibration.

Conclusion

^{18}F-FDG PET/CT restaging detects distant interval metastases in 8.3% of patients after chemoradiotherapy for esophageal cancer. The provided prediction score may stratify risk of developing interval metastasis, and could be used to prioritize additional restaging modalities for patients most likely to benefit.

INTRODUCTION

Esophageal cancer continues to affect more than 450,000 people annually, and is the sixth leading cause of cancer-related mortality worldwide[1]. Currently, surgical resection of the esophagus preceded by neoadjuvant chemoradiotherapy is the standard of care for patients with non-metastasized esophageal cancer[1–3]. Definitive chemoradiotherapy is the preferred approach for inoperable locally advanced esophageal cancer[4,5]. In consequence of the duration of chemoradiotherapy and subsequent waiting time to surgery, systemic interval metastases may develop that were not visible during baseline staging[6–8]. In these patients curative treatment is no longer possible[9].

Currently there is disagreement between guidelines whether all patients should be restaged after chemoradiotherapy[10–12]. In different international guidelines, routine restaging with computed tomography and integrated ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT) is not recommended[11], or partially recommended for patients with cT3-4 or cN1-3 tumors[12]. To the contrary the National Comprehensive Cancer Network advises restaging for all patients who receive preoperative chemoradiotherapy[10]. At present little is known about which patients are at risk of developing interval metastases.

Several small studies have assessed the role of ^{18}F-FDG PET/CT for pre-surgical restaging after neoadjuvant therapy, with reported incidence rates of interval metastases varying from 2% up to 26%[13,14]. However, most studies did not report diagnostic accuracy measures (i.e. sensitivity, specificity) and included only a small number of patients[6–8]. Also, studies that have assessed clinical predictors for interval metastases are scarce[15]. Accurate prediction of disease progression during and shortly after chemoradiotherapy would enable surveillance tailored to each patients underlying risk of developing systemic disease.

The aim of the current study was two-fold. First, to quantify the incidence of interval metastases after chemoradiotherapy, and evaluate the diagnostic performance of ^{18}F-FDG PET/CT for the detection of interval metastases in a large cohort of patients. Second, to identify pre-treatment clinical predictors for interval metastases.

METHODS

This retrospective study has been approved by the institutional review board of the MD Anderson Cancer Centre and the requirement to obtain informed consent was waived. The study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), the checklist from the Transparent Reporting of a multivariable prediction model

for Individual Prognosis or Diagnosis statement (http://www.tripod-statement.org)[16], and the checklist from the STAndards for the Reporting of Diagnostic accuracy studies (STARD) statement (http://www.stard-statement.org)[17].

Study population

Data from consecutive patients with biopsy-proven adenocarcinoma or squamous cell carcinoma of the esophagus that received chemoradiotherapy (with or without surgery) at the University of Texas MD Anderson Cancer Centre from January 2006 to July 2013 were extracted from a prospective collected departmental registry. Inclusion criteria were; non-metastatic potentially resectable esophageal cancer (cT1N+M0 or cT2-4aM0 with nodes in the anatomic region of a 2-field lymph node dissection), scheduled radiation dose of 45 or 50.4 Gy with concurrent chemotherapy, staging with ^{18}F-FDG PET/CT before and after chemoradiotherapy. Patients were excluded if the time interval between completion of chemoradiotherapy and ^{18}F-FDG PET/CT restaging was more than 3 months. The flow of patient selection is summarized in Fig. 1. Disease was staged in accordance with the 7th edition of the International Union Against Cancer for cTNM-classification[18]. Initial diagnostic work-up included endoscopy with biopsy, endoscopic ultrasound (including fine-needle aspiration if indicated), and ^{18}F-FDG PET/CT.

Treatment protocol

Chemoradiotherapy treatment generally consisted of a fluoropyrimidine (IV or oral) with either platinum- or taxane-based chemotherapy with concurrent radiotherapy (45 or 50.4 Gy in fractions of 1.8 Gy) (Table 1). Four to 6 weeks after completion of chemoradiotherapy, all patients underwent re-staging procedures and were discussed in multidisciplinary tumor conference. Patients that were deemed eligible for surgical treatment proceeded to esophagectomy. Surgical treatment consisted of transthoracic esophagectomy combined with lymphadenectomy.

Image acquisition and analysis

Patients were scanned with before and after completion of chemoradiotherapy on a dedicated PET/CT system (Discovery RX, ST, or STE; GE Medical Systems, Milwaukee [WI], USA). After fasting for at least 6 hours patients were injected with ^{18}F-FDG (555-740 MBq). An unenhanced CT was acquired for attenuation correction purposes (120 kV peaks, 300 mA, 0.5 seconds rotation, pitch of 1.375, slice thickness 3.75mm, and slice interval 3.27 mm). PET scans were acquired 60-90 minutes after administration of ^{18}F-FDG in either two-dimensional (2-D) or three-dimensional (3D) acquisition mode.

PET/CT interpretations rendered as part of the clinical care were extracted from the original PET/CT reports. All ^{18}F-FDG PET/CT images were reviewed by experienced nuclear medicine radiologists who were aware of patients' information and previous clinical findings. The images were evaluated for the presence of new lesions with non-physiological ^{18}F-FDG accumulation. Suspicious lesions on CT scans with increased focal ^{18}F-FDG uptake were indicated as malignant. ^{18}F-FDG PET/CT images were interpreted as positive for interval metastasis when new malignant lesions were found outside the anatomic dissection plane of an esophagectomy combined with a two-field lymphadenectomy.

Reference standard

A composite reference standard combining histologic proof and/or imaging follow-up was used to confirm the disease status of patients after restaging with ^{18}F-FDG PET/CT. Histologically verified PET/CT-positive lesions or lesions showing an increase in size or ^{18}F-FDG uptake on subsequent radiological follow-up were considered as true-positive (TP). Clinical follow-up was used as reference standard for patients with a negative ^{18}F-FDG PET/CT during restaging. Patients were followed every 3 months during the first year after treatment which included physical examination, blood tests, and ^{18}F-FDG PET/CT scans. The restaging ^{18}F-FDG PET/CT was considered false negative (FN) in case patients developed new metastatic disease within 3 months after the initial restaging ^{18}F-FDG PET/CT scan. Patients without confirmed systemic disease progression during follow up were considered as true-negative (TN).

Pre-treatment predictors

All patient, tumor, and treatment-related characteristics as reported in Table 1 were derived from the prospective collected departmental registry. Initial selection of predictors for interval metastasis detected by ^{18}F-FDG PET/CT restaging were pre-specified based on previous literature to prevent overfitting of the model. Categories were based on previously published cut-off points or estimated by receiver operating characteristic (ROC) curve analysis while maximizing sensitivity and specificity. Clinical factors available before initiation of treatment that have previously been identified as prognostic factors in esophageal cancer included gender[19], age (dichotomized into <65 and ≥65)[20], Histology (adenocarcinoma versus squamous cell carcinoma[3,20], histologic differentiation grade (good/moderate versus poor)[20,21], signet ring cell adenocarcinoma[22,23], EUS-based tumor length (dichotomized into <4.0cm and ≥4.0 cm)[24,25], nontraversability by EUS[15,24], tumor location (upper/middle versus distal or gastro-esophageal junction)[18], clinical T-status (T1b-2 versus T3-4)[19,20], clinical N status (N0 versus N1-3)[20,21], maximum lymph node diameter measured on axial CT image (<1.0cm versus ≥1cm)[26,27], and

^{18}F-FDG avid nodes at baseline PET[15]. The maximum standardized uptake value (SUV_{max}) of the primary tumor was dichotomized in <9.6 and ≥9.6 based on ROC curve analysis.

Statistics

Patient and treatment-related characteristics were described as frequencies with percentages for categorical variables, mean with standard deviation (SD) for normally distributed variables and median with range for skewed distributions. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of ^{18}F-FDG PET/CT for the detection of interval metastasis were calculated with 95% confidence interval (CI), on a per-patient basis. Kaplan-Meier curves were used to assess overall survival, and survival differences were evaluated using the log-rank test. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org, 'rms' package). A *p*-value of <0.05 was considered statistically significant.

Model development

The association between clinical characteristics and interval metastasis was studied using the chi-square test. All potential prespecified predictors for interval metastasis were included in a multivariable logistic regression model. The initial logistic regression model was reduced using backward stepwise elimination based on Akaike Information Criteria. The discriminative ability of the final model was evaluated using receiver operating characteristics curve analysis providing the concordance statistic (C-statistic). For internal validation the model was subjected to 200 bootstrap resamples to calculate the optimism of the model and the shrinkage factor, after which the C-statistic and the β-coefficients were adjusted. A practical scoring system was developed using the *beta*-regression coefficients of the predictors that remained in the final model. Calibration of the model was evaluated by plotting the mean predicted probability of interval metastasis versus the observed percentage of interval metastasis for each level of the prediction score.

RESULTS

In the study period a total of 783 patients diagnosed with esophageal cancer that met our inclusion and exclusion criteria underwent chemoradiotherapy followed by a restaging ^{18}F-FDG PET/CT scan (Fig. 1). The distribution of patient, tumor, and treatment-related characteristic are summarized in Table 1. The study population had a mean age of 62.5 years (SD: 10.6 years), and the majority of patients were male (86.2%). The predominant histologic tumor type was adenocarcinoma (85.8%), and the most common clinical tumor stage was cT3 (87.1%). The mean time interval between completion of chemoradiotherapy and ^{18}F-FDG PET/

CT restaging was 41.3 days (SD: 10.7). After completion of chemoradiotherapy, 450 (57.5%) patients underwent esophageal resection.

Diagnostic accuracy

In 109 of 783 (13.9%) patients new potential metastatic lesions were detected during PET/CT restaging. Of these patients 65 (TP: 65/783; 8.3%) were confirmed to have true metastatic disease by histology (n=21) or clinical follow up (n=44), and 44 were deemed to have false positive results (FP: 44/783; 5.6%) (see Fig. 2 and 3 for examples). The location and treatment of new metastatic lesions are presented in Table 2, and the location of false-positives in Fig. 1. Median overall survival of patients with interval metastasis was 6 months (95% CI: 4-8 months) compared to 59 months for patients without metastatic disease at restaging (47-70 months).

In patients with no evidence of interval metastasis after initial restaging with ^{18}F-FDG PET/CT, new metastatic lesions were identified in 22 (FN: 22/783; 2.8%) patients within 3 months of follow-up respectively (Fig. 1). The resulting overall per-patient sensitivity and specificity of ^{18}F-FDG PET/CT to detect interval metastasis was 74.7% (95% CI: 64.3-83.4%) and 93.7% (95% CI: 91.6-95.4%), respectively. Positive and negative predictive values of PET/CT were 59.6% (95% CI: 52.0-66.9%) and 96.8% (95% CI: 95.4-97.7%), respectively (Table 3).

Pre-treatment prediction of interval metastasis

The univariable association of clinical factors with interval metastasis after chemoradiotherapy are summarized in Table 1. After multivariable analysis, clinical nodal involvement (odds ratio [OR]: 2.91, 95% CI: 1.34-6.32), EUS-based tumour length ≥4 cm (OR: 2.68, 95% CI: 1.11-6.52), squamous cell tumor histology (OR: 1.65, 95% CI: 0.86-3.17) and baseline SUV_{max} ≥9.6 (OR: 1.66, 95% CI: 0.94-2.93) remained independently predictive for the occurrence of interval metastasis (Table 3). The discriminative ability of the final model was reasonable with an apparent C-statistic of 0.69, and 0.67 after adjustment for optimism. The shrinkage factor for the coefficients was 0.88. The adjusted β-coefficients of the prediction model for interval metastasis after shrinkage are presented in Table 3.

A practical prediction tool for the development of interval metastasis was developed based on the 4 predictors that remained in the final model. Based on the adjusted β-coefficients, each variable was converted into a corresponding number of points (multiplied by 2) rounded to its nearest integer. The total risk score was calculated by adding up the number of points obtained for each clinical predictor (cN status + EUS-based tumor length + tumor histology

+ baseline SUV_{max} = risk score; Table 4). In Table 4, also the corresponding observed risk for interval metastasis can be found for the different risk scores. The correspondence between the predicted risk of interval metastasis by the risk score and actual observed interval metastasis indicated good calibration (Fig. 4). In patients without interval metastasis after ^{18}F-FDG PET/CT restaging, the risk score was also significantly associated with survival (Fig. 5, p=0.001).

TABLE 1. Patient and treatment-related characteristics and their association with interval metastasis detected by ^{18}F-FDG PET/CT after neoadjuvant chemoradiotherapy

Characteristic		**All Patients** (n=783)		**Potentially resectable disease** (n=718)		**Systemic interval metastases** (n=65)		***p* value**
		n	%	n	%	n	%	
Gender	Male	675	86.2%	619	91.7%	56	8.3%	0.990
	Female	108	13.8%	99	91.7%	9	8.3%	
Age at diagnosis	<65 Years	425	54.3%	386	90.8%	39	9.2%	0.334
	≥65 years	358	45.7%	332	92.7%	26	7.3%	
Body mass index	<25 kg/m^2	390	49.8%	351	90.0%	39	10.0%	0.086
	≥25 kg/m^2	393	50.2%	367	93.4%	26	6.6%	
ECOG performance status	0	283	36.1%	262	92.6%	21	7.4%	0.501
	1-2	500	63.9%	456	91.2%	44	8.8%	
Weight loss	<10%	615	78.5%	570	92.7%	45	7.3%	0.056
	≥10%	168	21.5%	148	88.1%	20	11.9%	
Histology	AC	672	85.8%	621	92.4%	51	7.6%	0.076
	SCC	111	14.2%	97	87.4%	14	12.6%	
Histologic differentiation grade[a]	Good/Moderate	363	46.4%	339	93.4%	24	6.6%	0.111
	Poor	420	53.6%	379	90.2%	41	9.8%	
Signet ring cell adenocarcinoma	No	671	85.7%	617	92.0%	54	8.0%	0.529
	Yes	112	14.3%	101	90.2%	11	9.8%	
EUS-based tumor length	<4.0 cm	210	26.8%	204	97.1%	6	2.9%	0.001
	≥4.0 cm	573	73.2%	514	89.7%	59	10.3%	
Nontraversability by EUS	No	645	82.4%	595	92.2%	50	7.8%	0.228
	Yes	138	17.6%	123	89.1%	15	10.9%	
Tumour Location	Upper or middle	103	13.2%	93	90.3%	10	9.7%	0.309
	Distal or GEJ	680	86.8%	625	91.9%	55	8.1%	
SUV_{max} primary tumor at baseline	<9.6	410	60.0%	389	94.9%	21	5.1%	0.001
	≥9.6	373	40.0%	329	88.2%	44	11.8%	

TABLE 1 (continued). Patient and treatment-related characteristics and their association with interval metastasis detected by ^{18}F-FDG PET/CT after neoadjuvant chemoradiotherapy

Characteristic		**All Patients** (n=783)		**Potentially resectable disease** (n=718)		**Systemic interval metastases** (n=65)		***p* value**
		n	%	n	%	n	%	
Clinical T status (seventh)[b]	IB/II	90	11.5%	86	95.6%	4	4.4%	0.159
	III/IVa	693	88.5%	632	91.2%	61	8.8%	
Clinical N status (seventh)[b]	cN0	268	34.2%	260	97.0%	8	3.0%	<0.001
	cN+	515	65.8%	458	88.9%	57	11.1%	
Maximum Lymph node diameter[c]	<1.0 cm	542	69.2%	507	93.5%	35	6.5%	0.005
	≥1.0 cm	241	30.8%	211	87.6%	30	12.4%	
PET avid nodes at baseline	*m*N0	480	61.3%	448	93.3%	32	6.7%	0.037
	*m*N1	303	38.7%	270	89.1%	33	10.9%	
Total radiation dose (Gy)	45.0	49	6.3%	43	87.8%	6	12.2%	0.301
	50.4	734	93.7%	675	92.0%	59	8.0%	
Radiation treatment modality	3-D CRT	6	0.8%	5	83.3%	1	16.7%	0.492
	IMRT	505	64.5%	460	91.1%	45	8.9%	
	Proton Therapy	272	34.7%	253	93.0%	19	7.0%	
Chemotherapy regimen	Oxaliplatin / 5-FU	236	30.1%	223	94.5%	13	5.5%	0.286
	Docetaxel / 5-FU	265	33.8%	238	89.8%	27	10.2%	
	Capecitabine / 5-FU	167	21.3%	152	91.0%	15	9.0%	
	Other	115	14.7%	105	91.3%	10	8.7%	

[a:] Determined in pre-treatment biopsy [b:]Classified according to the 7th edition of the International Union Against Cancer (UICC) tumour-node-metastasis (TNM) classification[18]; [c:]Lymph node diameter was measured in the short axis by an experienced radiologists on the axial CT images; ECOG: Eastern Cooperative Oncology Group; AC: adenocarcinoma; SCC: squamous cell carcinoma; EUS: endoscopic ultrasonography; SUV: standardized uptake value.

TABLE 2. Location and treatment of interval metastasis, and false positives on ^{18}F-FDG PET/CT after neoadjuvant chemoradiotherapy

	n (%)
Location of interval metastasis	
Lung	18 (22)
Liver	17 (21)
Retroperitoneal	16 (20)
Bone	16 (20)
Supraclavicular LN	7 (8)
Other	7 (8)
Number of locations with recurrence	
1	49 (75)
>1	16 (25)
Type of management	
Treatment focused on tumor reduction	*40 (62)*
Chemotherapy	31 (78)
Radiotherapy	5 (12)
Chemoradiation	4 (10)
Best supportive care	*25 (38)*

TABLE 3. Diagnostic parameters of ^{18}F-FDG PET/CT for the detection of interval metastasis

Parameter	**^{18}F-FDG PET/CT**
Sensitivity (%) [95%CI]	65/87 (74.7%) [64.3-83.4]
Specificity (%) [95%CI]	652/696 (93.7%) [91.6-95.4]
Positive predictive value (%) [95%CI]	65/109 (59.6%) [52.0-66.9]
Negative predictive value (%) [95%CI]	652/674 (96.7%) [95.4-97.7]
Diagnostic accuracy	91.6%

TABLE 4. Risk prediction model for distant interval metastases

Characteristic	**Odds-ratio** (95% CI)		**Original regression coefficients**		**Adjusted regression coefficients**		**p-value**	**points**
Clinical nodal stage (N+ vs. N0)	2.91 (1.34-6.32)		1.069		0.940		0.007	2
EUS-based tumor length (≥4.0cm vs. <4.0cm)	2.68 (1.11-6.52)		0.988		0.869		0.029	2
Tumor histology (squamous cell vs. adeno-carcinoma)	1.65 (0.86-3.17)		0.501		0.440		0.132	1
SUV_{max} primary tumor at baseline (≥9.6 vs. <9.6)	1.66 (0.94-2.93)		0.509		0.448		0.078	1
Total number of points:	0	1	2	3	4	5	6	
Number of patients at risk:	81	31	140	94	165	225	47	
Risk of interval metastases (%):	1.1%	1.9%	3.2%	5.2%	8.5%	13.5%	20.5%	

Intercept: -4.425, shrinkage factor: 0.88

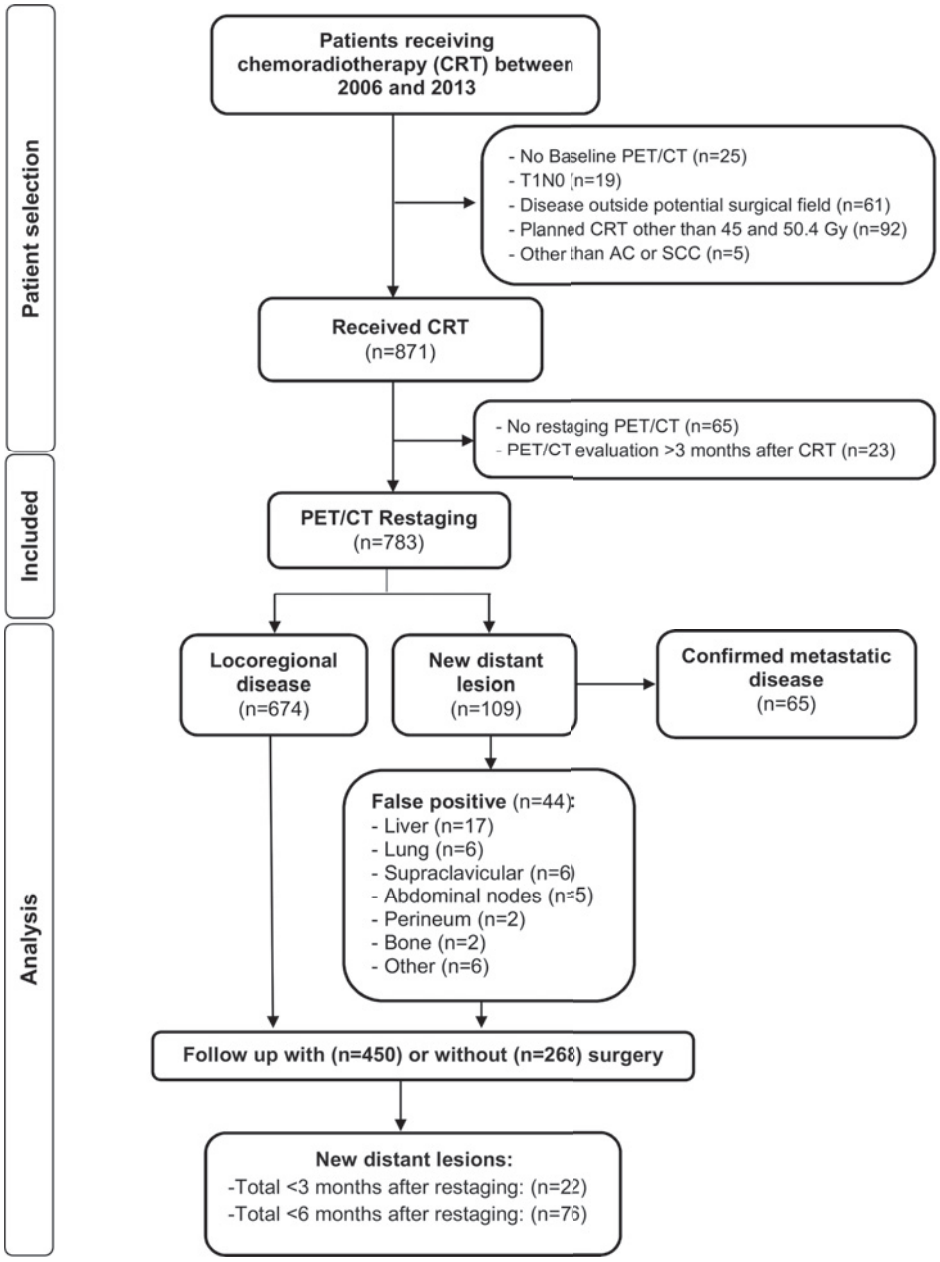

Figure 1. Flowchart of the study.

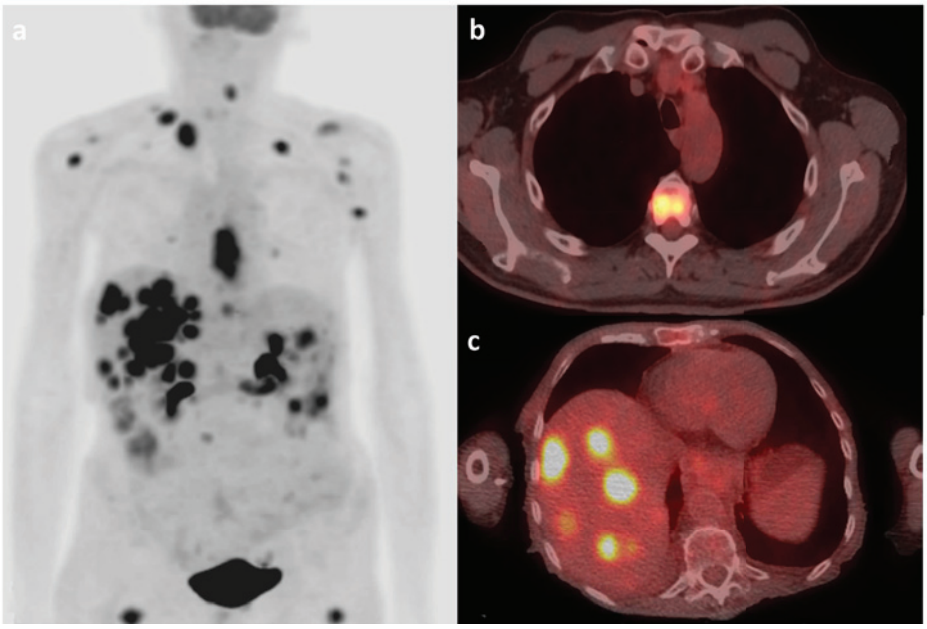

Figure 2. Examples of true positive metastatic lesions detected by ^{18}F-FDG PET/CT restaging. **(a/c):** 80-year-old woman with adenocarcinoma of the distal esophagus treated with chemoradiation. The maximum intensity projection PET image shows multiple hypermetabolic foci of the liver and multiple soft tissue lesions that were confirmed malignant with follow-up scans. **(b)**: 65-year-old male with squamous cell carcinoma of the distal esophagus who had undergone chemoradiotherapy. The PET/CT image showed ^{18}F-FDG accumulation in the liver and in the thoracic spine at T5. Follow-up CT showed disease progression.

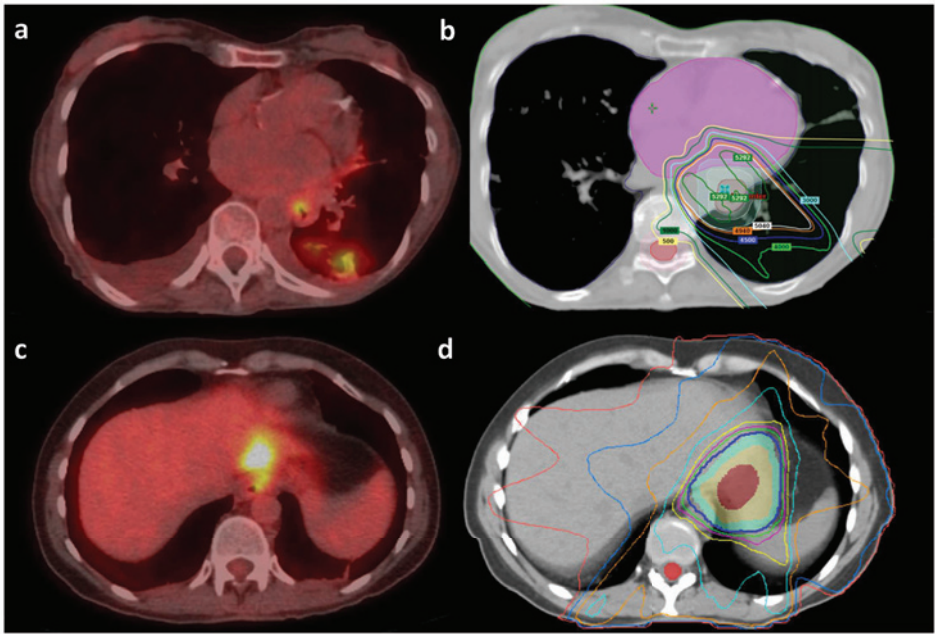

Figure 3. Examples of new non-malignant ^{18}F-FDG avid lesions detected by ^{18}F-FDG PET/CT restaging. **(a):** 78-year-old woman with squamous cell carcinoma of the esophagus treated with chemoradiation. The PET/CT image shows new opacities within the left lower with corresponding areas of ^{18}F-FDG activity. The new lesion was within the presumed radiation field **(b)** and the appearance was most compatible with radiation-induced pneumonitis (scan was regarded as 'true negative' for new metastatic disease). **(c):** 42-year-old female with adenocarcinoma of the distal esophagus who had undergone chemoradiotherapy. The PET/CT images show linear ^{18}F-FDG accumulation within the lateral aspect of the left hepatic lobe. The new lesion was within the presumed radiation field **(d)** and was thought to be related to radiation therapy changes, which was confirmed with a MRI scan (scan was regarded as 'false positive' as additional imaging was required to exclude metastatic disease).

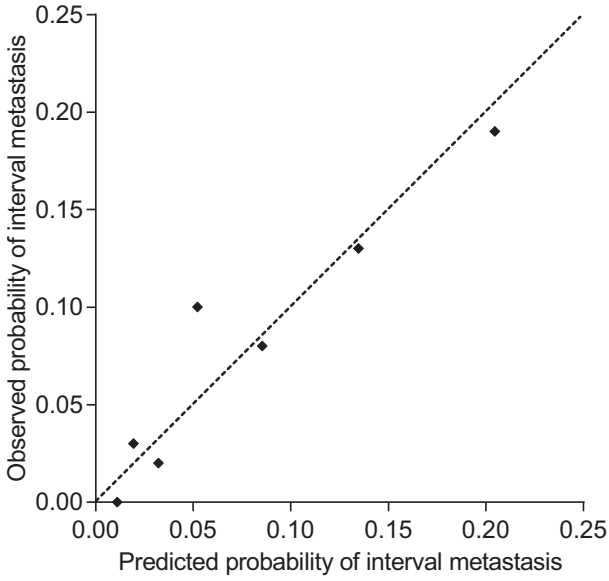

Figure 4. Calibration curve for predicted probability of interval metastasis for each unit of the risk score versus the observed frequency of interval metastasis.

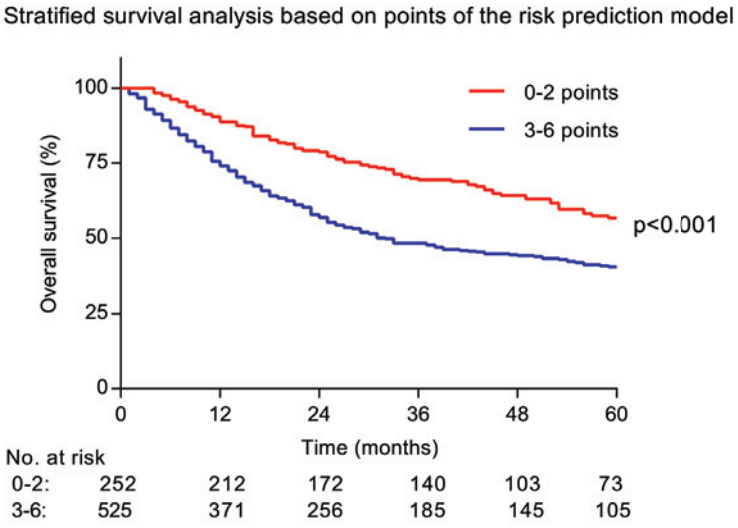

Figure 5. Risk prediction model for interval metastasis predicts overall survival in patients without interval metastasis after ^{18}F-FDG PET/CT restaging.

DISCUSSION

Findings in the current study demonstrate that ^{18}F-FDG PET/CT restaging after neoadjuvant chemoradiotherapy detects interval metastases in 8% of esophageal cancer patients, with a patient-based sensitivity and specificity of 75% and 94%, respectively. Independent risk factors for the development of interval metastases include clinical nodal involvement, EUS-based tumor length of ≥4 cm, squamous cell tumor histology, and baseline SUV_{max} of ≥9.6. Based on these findings, a prediction score was developed which may provide physicians a tool to objectively assess the risk of interval metastasis in patients with esophageal cancer.

Accurate preoperative detection of (interval) metastasis of esophageal cancer is crucial for optimal selection of patients suitable for surgery. In patients with accurately detected interval metastasis, surgery is expected to provide no benefit in terms of survival, but rather decrease quality of life due to highly morbid surgery with subsequent recovery time[28]. In this regard, the findings of the current study indicate that 8% of patients were spared a futile esophagectomy as a result of our routine ^{18}F-FDG PET/CT restaging protocol. Although previous studies on this topic have reported detection rates of interval metastasis ranging between 2% and 26%, guideline recommendations on restaging patients after neoadjuvant chemoradiotherapy for esophageal cancer remain contradictory[10–12].

The incidence of interval metastasis in the current study is consistent with the results of previous reports[6–8], however, there are some important other aspects of ^{18}F-FDG PET/CT restaging that should be considered. Our findings indicate that in 86% of patients no new lesion will be detected during restaging after chemoradiotherapy, implicating that limited impact on patient management is anticipated in the majority of patients. In another 6% of the patients restaging results in false positive findings introducing unnecessary imaging and biopsy procedures. It should be noted that this work-up is associated with additional costs and that biopsy procedures are not without risks[29].

Consequently, a more individualized application of ^{18}F-FDG PET/CT restaging could reduce the number of unbeneficial diagnostic tests. Yet, little is known about what patients are at risk for developing interval metastases, and the small number of patients in the previous mentioned studies precludes assessment of predictors for interval metastasis after neoadjuvant therapy[6–8,15]. These findings encouraged us to develop a risk prediction score for interval metastases, that may guide a more targeted application of ^{18}F-FDG PET/CT restaging. This may especially be of interest for hospitals/regions with limited resources that have not yet

implemented ^{18}F-FDG PET/CT restaging in their routine clinical practice due to associated costs.

The proposed risk score – based on well-recognized prognostic factors[3,20,21,24,25,30] – has reasonable predictive value and may guide clinical decision making. The data indicate that patients with low scores have limited risk of interval metastases, and that in these patients a restaging ^{18}F-FDG PET/CT may be safely omitted without subjecting the patient to the risks of further diagnostic tests. Increasing the threshold for restaging patients with ^{18}F-FDG PET/CT based on the proposed risk score will result in a further reduction of unnecessary additional scans and biopsies (false positives), however, at the potential cost of missing interval metastasis (false negatives). Determining an appropriate threshold to initiate restaging will depend on patients' and physicians' judgments about the harm of missed interval metastasis versus unnecessary diagnostic tests and available resources.

The relatively high incidence (11%) of early disease progression already within 6 months after restaging (Fig. 1) suggests that small distant metastases, which are not detected by ^{18}F-FDG PET/CT, may already have occurred at the time of restaging[31]. This indicates that while ^{18}F-FDG PET/CT detects a substantial proportion of interval metastasis it is sometimes insufficient to detect all early disease progression. Therefore, one may consider close monitoring of high-risk patients with additional (perioperative) restaging. This suggestion is supported by our finding that the risk score was also predictive for survival after initial restaging.

In the context of clinical decision-making with regard to those patients who are most likely to benefit from an esophageal resection after chemoradiotherapy, the prediction of pathological response to neoadjuvant therapy may be another motivation to perform ^{18}F-FDG PET/CT restaging. It has been suggested that preoperative identification of patients with a pathologic complete response – aided by information derived from ^{18}F-FDG PET/CT – could enable a wait-and-see approach with omission of surgery[19,32]. However, currently uncertainty continues to exist over the clinical benefit of ^{18}F-FDG PET/CT with regard to the accuracy for differentiating between residual tumor and therapy induced inflammation after chemoradiotherapy[33–35]. Other reasons to perform a restaging scan includes surgical planning (notable for GEJ tumors).

As discussed, the false positive rate of 6% during ^{18}F-FDG PET/CT restaging was substantial, with the lungs and liver as the most frequent affected sites. This confirms previous findings in literature, with reported false positive rates ranging between 0% and 10%[6,36] and liver and lung as most common affected sites[29,37]. This is likely caused by radiation-induced disease that

may falsely indicate disease progression (Fig. 2 and 3). Previous studies evaluating new FDG-avid hepatic lesions within the presumed radiation field of patients with esophageal cancer demonstrated that these lesions generally reflect radiation-induced liver disease rather than metastatic disease[37–39]. Evaluation of radiation fields may, therefore, aid in the assessment of restaging ^{18}F-FDG PET/CT scans and further clinical decision-making[37].

Potential limitations of this study are that it used follow-up information as reference standard, which is challenging because follow-up should be long enough to allow hidden cases of disease to progress to a detectable stage, while it should be short enough to prevent new cases that develop after restaging to be detected. Because the length of follow-up to determine disease-status is arbitrary, reported diagnostic accuracy measures may vary in case of different follow-up lengths. Second, histological biopsy was not performed in all patients with suspected interval metastasis, which may have introduced reference test bias. Third, quantitative imaging values such as SUV may be biased by many factors related to clinical protocols and PET system settings, many of which are center or manufacturer depended. Therefore, future studies that use quantitative imaging for prognostic modeling are encouraged to control biases through standardization of imaging procedures by using harmonization programs (e.g. Quantitative Imaging Biomarkers Alliance[40]. Furthermore, the current study represents a single-institution analysis where findings in general may not be generalizable to other centers. Therefore, external validation of the developed risk prediction score is recommended to determine generalizability[41].

Despite the aforementioned limitations, major strengths of this study include that it is the largest study so far to assess the diagnostic performance of ^{18}F-FDG PET/CT for the detection of interval metastases. Furthermore, it provides the first clinically applicable risk prediction score for interval metastasis after chemoradiotherapy for esophageal cancer.
^{18}F-FDG PET/CT restaging detects true distant interval metastases in 8.3% of patients after chemoradiotherapy for esophageal cancer. The provided prediction score stratifies risk of developing interval metastasis, and could be used to prioritize additional restaging modalities for patients most likely to benefit. Centers that do not routinely perform ^{18}F-FDG PET/CT restaging, should at least consider to scan patients high at risk of interval metastases.

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4

Staging and role of neoadjuvant chemoradiotherapy in clinical T2N0M0 esophageal cancer: a population-based cohort study

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ABSTRACT

Objective

The aim of this population-based cohort study was to determine whether the addition of neoadjuvant chemoradiotherapy (nCRT) to surgery is associated with improved pathologic outcomes and survival in patients with cT2N0M0 esophageal cancer.

Methods

Patients who underwent nCRT followed by surgery or surgery alone for cT2N0M0 esophageal cancer were identified from The Netherlands Cancer Registry database (2005-2014). Accuracy of clinical staging was assessed using the resection specimen as gold standard. After propensity score matching, influences of both treatment strategies on radical resection (R0) rates and overall survival were compared.

Results

In total 533 patients were included; 353 underwent nCRT followed by surgery and 180 underwent surgery alone. In the nCRT group 32% of patients achieved a pathologic complete response. Clinical understaging was observed in 62% of the patients in the surgery alone group based on pT-stage (n=30, 27%), pN-stage (n=26, 23%), or both (n=55, 50%). Propensity score matching resulted in 78 patients who underwent nCRT plus surgery versus 78 who underwent surgery alone. In the nCRT group radical resections were more frequently observed (99% vs. 89% p=0.031) and resulted in improved 5-year overall survival (46% vs. 33%, p=0.017).

Conclusion

In this population-based study, clinical staging of cT2N0M0 esophageal cancer was highly inaccurate. Compared to surgery alone, neoadjuvant chemoradiotherapy was associated with higher radical resection rates and improved overall survival.

INTRODUCTION

Esophageal carcinoma is the sixth most common cause of cancer-related death globally, and the incidence of esophageal carcinoma is increasing[1,2]. For patients with locally advanced non-metastatic esophageal cancer, multimodality treatment with neoadjuvant chemoradiotherapy (nCRT) followed by surgery has shown to improve 5-year survival with 14% compared to a surgery alone approach[3, 4]. However, controversy still exists regarding the optimal treatment strategy for patients with clinical T2N0M0 (cT2N0M0) esophageal cancer.

Clinical T2 esophageal cancer represents an anticipated early stage disease. In the absence of nodal disease during clinical staging, a surgery alone approach may be regarded as the designated treatment for these tumors[5,6]. Unfortunately, current preoperative staging of patients with cT2N0M0 esophageal cancer is notoriously imprecise, and studies have reported clinical understaging rates between 27% and 56% for cT2N0M0 esophageal cancer[5-11].

Due to the limitations of the current clinical staging techniques, a multimodality treatment approach for cT2N0M0 esophageal cancer patients is recommended by several studies[7, 8, 10, 12]. However, despite clinical understaging of lymph node metastasis and tumor stage, other studies could not confirm a survival benefit of a multimodality treatment approach compared to a surgery alone approach for cT2N0M0 esophageal cancer[5,6,11,13-15]. Moreover, concerns have been raised with regard to the toxicity of nCRT that could result in an increased risk of postoperative complications[16-19].

The available studies that assess whether nCRT adds any benefit to patients with cT2N0M0 esophageal cancer are equivocal. Therefore, the aim of the present nation-wide multi-centre study was to determine whether the addition of nCRT to surgery is associated with improved pathologic outcomes, postoperative mortality, and survival in a large cohort of patients with cT2N0M0 esophageal cancer.

METHODS

Data collection and study population

This nation-wide population-based cohort study was conducted with data from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.8 million inhabitants. The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL) and is mainly based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Information on patient and treatment-related characteristics such as gender, date of birth, tumor histology, tumor stage,

and primary treatment are routinely obtained from medical records by trained data managers using the NCR registration and coding manual. Information on vital status was obtained by annual linkage with the Municipal Administrative Databases, in which all deceased and emigrated persons in the Netherlands are registered. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

Patients diagnosed with clinical T2 and N0 histologically proven primary esophageal adenocarcinoma or squamous cell carcinoma, who underwent esophagectomy with curative intent in The Netherlands from 2005 through 2014 were eligible for this study. Inclusion criteria consisted of patients who received nCRT followed by esophagectomy or esophagectomy alone.

Clinical and pathological staging

After initial diagnosis of esophageal cancer, each patient underwent further investigations needed for adequate staging. In the Netherlands, pretreatment clinical staging includes endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) of thorax and abdomen, or integrated ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scanning. Tumors were staged according to the International Union Against Cancer (UICC) TNM classification, that was valid at the time of diagnosis. Patients diagnosed between 2005 and 2009 were staged using the 6th edition, and those diagnosed between 2010 and 2014 according to the 7th edition[20]. Clinical and pathological T and N stage were translated according to the 7th edition for this study for uniformity purposes.

Treatment

In the last decade, nCRT according to the CROSS regimen (carboplatin [AUC 2 mg/mL per min] and paclitaxel [50mg/m2] weekly during 5 weeks and concurrent radiotherapy [41.4 Gy in 23 fractions of 1.8 Gy]) became standard of care for patients with locally advanced esophageal cancer in the Netherlands. In general, eligible patients had a WHO performance status ≤2, and did not lose >10% of their body weight. The surgical procedure consisted of a transthoracic or transhiatal esophagectomy with lymphadenectomy and gastric tube reconstruction with cervical or intrathoracic anastomosis.

Statistical analyses and outcome measures

To estimate the accuracy of clinical staging in the surgery alone group, pathologic staging data were used to calculate the respective rates of clinical T- and N- understaging and overstaging. Due to the use of induction therapy in the nCRT group clinical T- and N- underderstaging or overstaging could not be truly assessed. The postoperative pathological stages were reported.

Categorical data are presented as numbers and percentages and continuous data are expressed as mean ± standard deviation (SD) or median (range). To determine differences between the two treatment groups regarding baseline characteristics and outcomes (i.e. surgical radicality and 90-day mortality) the Chi square test was used for categorical variables, and Student's t test or Mann-Whitney *U*-test for parametric and non-parametric continuous variables, respectively. Kaplan-Meier survival curves were constructed for both treatment groups, and compared using the log-rank test. Second Kaplan-Meier survival curves were constructed for patients in the surgery alone group with a pT2N0-stage versus >pT2N0-stage and for patients in the nCRT group with a pT2N0-stage, <pT2N0-stage or >pT2N0-stage.

In order to avert the effect of confounding influences of covariates on the assessed outcomes between the two study groups (nCRT versus surgery alone), propensity score matching was performed to create comparable groups. First, a propensity score was calculated for each patient using logistic regression, based on available patient and treatment-related characteristics that may influence prognosis (i.e. age, gender, history of previous malignancy, histology, surgical approach, referral for esophagectomy, year of diagnosis, hospital volume; Table 1). Subsequently, nearest-neighbor (1:1; 'greedy') propensity score matching without replacement was performed in which the within-pair difference was minimized by setting a caliper of 0.25 of the standard deviation of the logit of the propensity score. All analyses were performed using IBM SPSS Statistics Version 23.0 for Windows (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' package). To manage missing data, a complete case analysis was carried out. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Study population and characteristics

The NCR identified 581 patients diagnosed with cT2N0M0 esophageal adenocarcinoma or squamous cell carcinoma, who underwent esophagectomy with curative intent in The Netherlands from 2005 through 2014. A total of 48 patients were excluded because of neoadjuvant chemotherapy (n=24) or radiotherapy (n=2), and due to missing data in any of

the studied variables (n=22). The remaining 533 patients were included in this study; 353 patients received nCRT, and 180 patients underwent surgery alone (Table 1).

In both the nCRT group and the surgery alone group, most patients were male (n=259 [73%] vs. n=138 [77%]), and were predominantly diagnosed with adenocarcinoma (n=277, [79%] vs. n=145 [81%]). Patients in the surgery alone group had a higher age compared to patients in the nCRT group (mean 66.0 vs. 63.5 years, p=0.005). Patients who received nCRT were diagnosed in more recent years compared to patients in the surgery alone group (2011-2014; n=277 [79%] vs. n=28 [16%]), and underwent their resection more often in a hospital with a high surgical volume (>20; n=193 [55%] vs. n=76 [42%]). In order to compensate for the differences in baseline between the nCRT group and the surgery alone group, propensity score matching was performed. After propensity score matching 78 versus 78 patients remained, and all baseline variables were equally balanced (Table 1).

T- and N- staging

In the original cohort the true pretreatment pathological stage of the 353 patients in the nCRT group, could not be assessed due to the use of induction therapy. However, in this group clinical understaging occurred in at least 109 (31%) patients, based on ypT-stage (n=44, 40%), ypN-stage (n=37, 34%), or both (n=28, 26%) (Table 2). A pathological complete response (ypT0N0) was observed in 113 patients (32%) (Table 2). Postoperative pathological staging of the 180 patients in the surgery alone group demonstrated that 69 (38%) patients had accurate pretreatment staging (Table 2). The other 111 (62%) patients were clinically understaged based on pT-stage (n=30, 27%), pN-stage (n=26, 23%), or both (n=55, 50%) (Table 2). No clinical overstaging was reported.

Pathologic T- and N-stage after propensity score matching are presented in Table 3. Pathologic downstaging was more frequently observed in patients who underwent nCRT compared to surgery alone (p<0.001).

Radicality

In the original cohort a microscopically radical (R0) resection was achieved in 344 (98%) patients in the nCRT group, and in 158 (88%) patients in the surgery alone group (p<0.001). Among the 31 (6%) patients with no radical resection (R1), 28 (90%) patients were clinically understaged (>(y)pT2N0). After propensity score matching nCRT remained associated with higher R0 resection rates compared to surgery alone (99% [n=77] vs. 89% [n=69] p=0.031, respectively) (Table 3).

Postoperative mortality

Postoperative 30-day and 90-day mortality before and after propensity score matching are presented in Table 3. In the original cohort the total 90-day mortality rate after esophagectomy was 2% (n=7) in the nCRT group, and 9% (n=17) in the surgery alone group (p=<0.001). After propensity score matching there was no significant difference in total 90-day mortality between the nCRT and surgery alone group (4%[n=3] vs. 10% [n=8], p=0.132, respectively).

Overall survival

In the original cohort median follow-up of all patients was 32.6 months [range 0-141]. Overall 1-, 3-, and 5-years survival rates were 86%, 62%, and 48% in the nCRT group and 76%, 51% and 35% in the surgery alone group (log-rank test p=0.001) (Table 3). Kaplan-Meier survival curves showed that in the surgery alone group clinically understaged patients (>pT2N0) had a significant worse overall survival compared to clinically true staged (pT2N0) patients (log-rank test p<0.001, Figure 1). In the nCRT group, patients with >ypT2N0 disease at pathology had a significant worse survival compared to patients with ypT2N0 or yp≤T2N0 (log-rank test p<0.001, Figure 1).

After propensity score matching, median follow-up of all patients was 40.4 months [range 0-133]. Overall 1-, 3-, and 5-years survival rates were 91%, 62%, and 46% in the nCRT group and 74%, 51% and 33% in the surgery alone group (log-rank test p=0.017, Figure 2, Table 3)).In a subgroup analysis of patients with adenocarcinoma, nCRT remained significantly associated with improved overall survival compared to the surgery alone group (log-rank test p=0.019)

TABLE 1. Comparison of baseline characteristics of 533 patients who underwent neoadjuvant chemoradiotherapy or surgery alone for cT2N0M0 esophageal cancer, before and after propensity score matching

	Original cohort					**Propensity score matched cohort**				
	nCRT + surgery		**Surgery**			**nCRT + surgery**		**Surgery**		
	n=353	**(%)**	**n=180**	**(%)**	**p-value**	**n=78**	**(%)**	**n=78**	**(%)**	**p-value**
Age [mean ± SD] *	63.5	±9.4	66.0	±9.7	0.005	65.1	±9.0	67.0	±10.0	0.205
Gender*					0.409					1.000
Male	259	(73)	138	(77)		63	(81)	63	(81)	
Female	94	(27)	42	(23)		15	(19)	15	(19)	
Malignancy history*					0.184					0.556
No	295	(84)	142	(79)		60	(77)	63	(81)	
Yes	58	(16)	38	(21)		18	(23)	15	(19)	
Histology*					0.575					0.525
Squamous cell carcinoma	76	(22)	35	(19)		15	(19)	12	(15)	
Adenocarcinoma	277	(79)	145	(81)		63	(81)	66	(85)	

TABLE 1 (continued). Comparison of baseline characteristics of 533 patients who underwent neoadjuvant chemoradiotherapy or surgery alone for cT2N0M0 esophageal cancer, before and after propensity score matching

	Original cohort					**Propensity score matched cohort**				
	nCRT + surgery		**Surgery**			**nCRT + surgery**		**Surgery**		
	n=353	**(%)**	**n=180**	**(%)**	**p-value**	**n=78**	**(%)**	**n=78**	**(%)**	**p-value**
Surgical approach*					<0.001					1.000
Transhiatal	147	(42)	116	(64)		47	(60)	47	(60)	
Transthoracal	206	(58)	64	(36)		31	(40)	31	(40)	
Referral for esophagectomy*					0.004					0.326
No	119	(34)	84	(47)		34	(44)	28	(36)	
Yes	234	(66)	96	(53)		44	(56)	50	(64)	
Year of diagnosis*					<0.001					0.814
2005-2007	9	(3)	70	(39)		9	(12)	8	(10)	
2008-2010	67	(19)	82	(46)		38	(49)	42	(54)	
2011-2014	277	(79)	28	(16)		31	(40)	28	(36)	
Hospital volume*					<0.001					0.931
≤10	46	(13)	53	(29)		12	(15)	11	(14)	
11-20	114	(32)	51	(28)		22	(28)	24	(31)	
>20	193	(55)	76	(42)		44	(56)	43	(55)	

Note. Data are numbers of patients with percentages in parentheses. *Variables used for propensity score matching. nCRT: neoadjuvant chemoradiotherapy; SD: standard deviation

TABLE 2. Pathological TN-stage of 533 patients who underwent neoadjuvant chemoradiotherapy or surgery alone for cT2N0M0 esophageal cancer

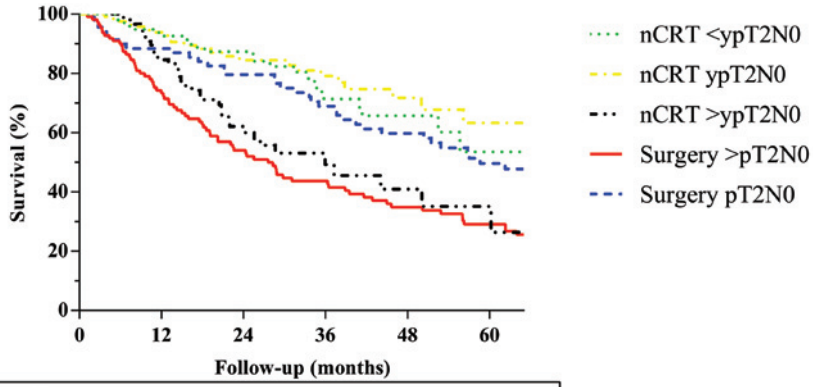
	nCRT + surgery		**Surgery**	
	n=353	**(%)**	**n=180**	**(%)**
(y)pTN stage				
T0N0	113	(32)	n.a.	-
T1N0	0	(0)	0	(0)
T2N0	131	(37)	69	(38)
T3-4N0	44	(12)	30	(17)
T0N+	9	(3)	0	(0)
T1N+	0	(0)	0	(0)
T2N+	28	(8)	26	(14)
T3-4N+	28	(8)	55	(31)
(y)pTN stage grouped				
<T2N0	113	(32)	0	(0)
T2N0	131	(37)	69	(38)
>T2N0	109	(31)	111	(62)

Note. Data are numbers of patients with percentages in parentheses.
nCRT: neoadjuvant chemoradiotherapy

TABLE 3. Comparison of outcomes after treatment of 533 patients who underwent neoadjuvant chemoradiotherapy or surgery alone for cT2N0M0 esophageal cancer, before and after propensity score matching.

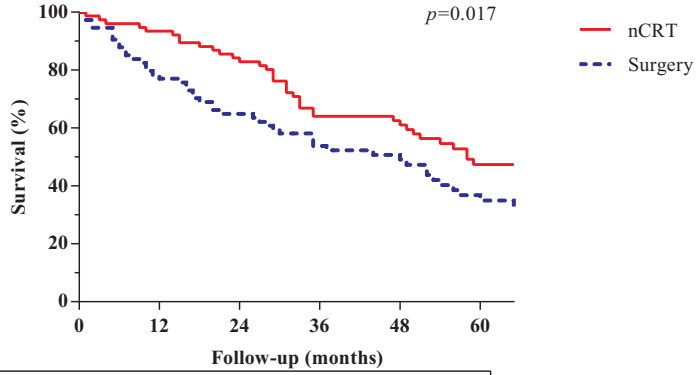
	Original cohort					**Propensity score matched cohort**				
	nCRT + surgery		**Surgery**			**nCRT + surgery**		**Surgery**		
	n=353		**n=180**		**p-value**	**n=78**		**n=78**		**p-value**
Pathologic T-stage (%)*					<0.001					<0.001
(y)pT0	122	(35)	0	(0)		28	(36)	0	(0)	
(yp)T1	0	(0)	0	(0)		0	(0)	0	(0)	
(y)pT2	159	(45)	95	(53)		31	(39)	39	(50)	
(y)pT3	71	(20)	82	(46)		19	(24)	37	(47)	
(y)pT4	1	(.3)	3	(2)		0	0	2	(3)	
Pathologic N-stage (%)*					<0.001					<0.001
(y)pN0	288	(82)	99	(55)		66	(85)	39	(50)	
(y)pN1	49	(14)	47	(26)		9	(12)	23	(30)	
(y)pN2	13	(4)	25	(14)		2	(3)	12	(15)	
(y)pN3	3	(1)	9	(9)		1	(1)	4	(5)	
Lymph node yield, median (range)	16	(1-46)	13	(0-47)	<0.001	13	(1-33)	14	(3-47)	0.807
Radicality of resection (%)					<0.001					0.031
R1	9	(2)	22	(12)		1	(1)	9	(11)	
R0	344	(98)	158	(88)		77	(99)	69	(89)	
Postoperative death (%)										
30-day mortality	7	(2)	11	(6)	0.013	3	(4)	6	(8)	0.303
90-day mortality	7	(2)	17	(9)	<0.001	3	(4)	8	(10%)	0.132
% overall survival					<0.001					0.017
1-year	86%		76%			91%		74%		
3-year	62%		51%			62%		51%		
5-year	48%		36%			46%		33%		

Note. Data are numbers of patients with percentages in parentheses unless indicated otherwise. *Pathological stage classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification. nCRT: neoadjuvant chemoradiotherapy.



Number at risk:						
nCRT						
<ypT2N0	113	69	48	25	11	5
ypT2N0	131	74	51	30	16	11
>ypT2N0	109	49	23	12	5	3
Surgery						
pT2N0	69	60	53	43	36	27
>pT2N0	111	72	49	38	31	24

Figure 1. Kaplan-Meier curves comparing overall survival in the original cohort of patients in the surgery alone group whom were clinically understaged (>pT2N0, red line) versus patients with a clinical true stage (pT2N0, blue line) (log-rank test $p<0.001$), and patients treated with nCRT with >ypT2N0 (black line) versus <ypT2N0 (green line) (log-rank test $p<0.001$), ypT2N0 (yellow line) (log-rank test $p<0.001$).



Number at risk:						
nCRT	78	71	63	45	41	26
Surgery	78	58	48	37	28	18

Figure 2. Kaplan-Meier curves comparing overall survival after propensity score matching of patients who underwent neoadjuvant chemoradiotherapy (nCRT, red line) or surgery alone (blue line) for cT2N0M0 esophageal cancer.

DISCUSSION

In this nationwide multi-center cohort study, outcomes of nCRT were compared to a surgery alone approach for patients with cT2N0M0 resectable esophageal cancer. Clinical understaging was seen in 62% of patients in the surgery alone group. In the nCRT group 32% of patients achieved a pathologic complete response. These findings likely explain the observed increased R0 resection rates and increased overall survival in favor of the nCRT group.

Accurate staging of esophageal cancer is essential to select patients for an appropriate treatment strategy. The present study, however, demonstrates that staging of patients with cT2N0M0 esophageal cancer is highly inaccurate, with 62% of the patients in the surgery alone group being clinically understaged. This finding is in line with other studies that reported clinical understaging rates between 27% and 56% for cT2N0M0 tumors[5-11]. Furthermore, the current study found that clinically understaged patients in the surgery alone group had worse overall survival compared to patients with accurate clinical staging in the surgery alone group. Due to the risk of clinical understaging, along with the demonstrated survival benefit of nCRT for locally advanced esophageal cancer[4,21], a multimodality treatment approach appears preferable for cT2N0M0 esophageal cancer patients.

A drawback of nCRT is the associated toxicity which may negatively affect quality of life, and can result in increased postoperative morbidity and mortality[10,14,22,23]. Therefore, it has been suggested that a multimodality approach for patients with cT2N0M0 disease based on the argument of clinical understaging alone is not the rightful treatment strategy for these patients[5]. However, the CROSS trial found no difference in postoperative morbidity and mortality between patients treated with nCRT and surgery alone[21]. Unfortunately, the current study could not asses postoperative morbidity, as data regarding postoperative outcomes were not available in the Netherlands Cancer Registry database.

In the current study, analysis of postoperative mortality demonstrated no significant association between type of treatment and the risk of 90-day mortality (p=0.132). However, 90-day mortality was relatively high after surgery alone. In that regard the introduction of nCRT and centralization of esophagectomies in the Netherlands occurred simultaneously, which may have improved postoperative mortality rates in favor of the nCRT group. Also, it may have occurred that patients were scheduled for surgery alone because they were unfit for multimodality treatment. These patients represent those in whom there may have been a relatively high risk of postoperative mortality, negatively affecting the mortality rate in the surgery alone group. Moreover, our study may have underestimated the effect of nCRT on

postoperative mortality, because patients who were treated with nCRT and did not proceed to surgery were not included in this analysis. Therefore, this study could not assess mortality during or immediately following nCRT prior to surgical resection. However, previous reported numbers of patients that do not proceed to surgery after CROSS are low (0.6%, 1/171)[21].

The current study shows that patients in the nCRT group had a significantly higher radical resection rate compared to patients in the surgery alone group (99% vs. 89%, respectively). Furthermore, a significant increase in overall survival was shown for patients treated with nCRT compared to patients in the surgery alone group. These results underline the findings of a recent large population based study that found a worse overall survival for understaged cT2N0M0 patients treated with surgery alone compared to patients who underwent neoadjuvant chemo(radio)therapy[12].

On the other hand, other studies did not demonstrate a survival benefit of a multimodality treatment approach compared to a surgery alone approach for cT2N0M0 patients[5,6,11,13-15]. However, many of these studies have significant shortcomings. Firstly, due to a low incidence of cT2N0M0 stage patients in esophageal cancer the majority of single center retrospective studies only included a small number of patients (between 27 up to 71 patients)[7,8,10,11,13] resulting in insufficient study power to perform a reliable survival analysis. Second, some studies did not use adequate methods to control for well-known confounders such as patient- and treatment-related characteristics[10,11]. Third, one larger study corrected for pathological tumor and node stage in multivariable analysis, which eliminates the potential effect of nCRT on the relationship between downsizing (lower pTN stage) and survival[6]. Fourth, many studies used second-best neoadjuvant therapies such as radiotherapy alone[15], or nCRT including the chemotherapeutic component fluorouracil/cisplatin[5,14] which may be inferior with regard to safety and postoperative mortality in comparison with the chemotherapeutic regimen used in the current study (paclitaxel/carboplatin according to the CROSS-trial)[21,24].

Important limitations of this study that should be acknowledged is its retrospective character and lack of randomization. In order to adjust for the potentially resulting confounding bias, propensity score matching using known (potential) confounders was performed to improve the comparability between the two groups. Propensity score matching is considered as a high quality method to adjust for such known (potential) confounding factors[25]. However, due to the inclusion of two groups receiving treatment partly in different time periods it is possible that variables that are difficult to measure (e.g. improvement in staging techniques, patient selection) were not equivalent, which to some extent may explain the differences between

the two groups. In addition, it was not possible to correct for other potential confounding factors (e.g. minimal invasive surgery, specific comorbidities, performance status, and tumor differentiation) as they were not yet registered in the Netherlands Cancer Registry database. Strengths of this study include the relatively large sample size compared to many previous comparative studies. Furthermore, the Netherlands Cancer Registry is known for its reliable and objective data collection. Moreover, this is one of the first studies that directly compares a highly recommended multimodality treatment regimen (CROSS) with a surgery alone approach for patients with cT2N0M0 esophageal cancer.

In conclusion, the current population-based study confirms that clinical staging of T2N0M0 esophageal cancer is highly inaccurate. Until clinical staging improves significantly, the results of this study suggest that neoadjuvant chemoradiotherapy may be preferable as treatment strategy for cT2N0M0 esophageal cancer patients.

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5

Diagnostic performance of ^{18}F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis

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ABSTRACT

Objective

The aim of this study was to assess the diagnostic performance of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and integrated ^{18}F-FDG PET-computed tomography (CT) for diagnosing recurrent esophageal cancer after initial treatment with curative intent.

Methods

The PubMed, Embase and Cochrane library were systematically searched for all relevant literature using the keywords '^{18}F-FDG PET' and 'esophageal cancer', and synonyms. Studies examining the diagnostic value of ^{18}F-FDG PET or integrated ^{18}F-FDG PET/CT, in either routine clinical follow-up or in symptomatic patients suspected of recurrent esophageal cancer were deemed eligible for inclusion. The primary outcome was the presence of recurrent esophageal cancer as determined by histopathological biopsy or clinical follow-up. Risk of bias and applicability concerns were assessed using the QUADAS-2 tool. Sensitivities and specificities of individual studies were meta-analyzed using bivariate random-effects models.

Results

Eight eligible studies were included for meta-analysis, comprising a total of 486 patients with esophageal cancer that underwent ^{18}F-FDG PET or PET/CT after previous treatment with curative intent. The quality of the included studies assessed by the QUADAS-2 tool was considered reasonable; there were few concerns with regard to the risk of bias and applicability. Integrated ^{18}F-FDG PET/CT and standalone ^{18}F-FDG PET were used in 4 and 3 studies, respectively. One other study analyzed both modalities separately. In 4 studies ^{18}F-FDG PET or PET/CT was performed as part of routine follow-up, whereas in 4 other studies the diagnostic test was performed on indication during clinical follow-up. Pooled estimates of sensitivity and specificity for ^{18}F-FDG PET and PET/CT in diagnosing recurrent esophageal cancer were 96% (95% confidence interval [CI]: 93%-97%) and 78% (95% CI: 66%-86%), respectively.

Conclusion

^{18}F-FDG PET and PET/CT are reliable imaging modalities with a very high sensitivity and moderate specificity for detecting recurrent esophageal cancer after treatment with curative intent. The use of ^{18}F-FDG PET or PET/CT particularly allows for a minimal false negative rate. However, histopathological confirmation of ^{18}F-FDG PET or PET/CT suspected lesions remains required, since a considerable false positive rate is noticed.

INTRODUCTION

Surgical resection of the esophagus with en-bloc lymphadenectomy remains the cornerstone of treatment with curative intent for patients with localized esophageal cancer[1]. A multimodal approach is increasingly applied as strong evidence exists for a survival benefit of 7-13% with neoadjuvant chemo(radio)therapy over surgery alone[2,3]. Overall 5-year survival rates of patients with esophageal cancer who are treated with curative intent remain relatively poor (34-47%)[3,4]. This is mainly attributable to the high incidence of recurrent disease early after treatment ranging from 45% to 53%[5-7]. Most recurrences occur within the first two years after surgery with median time to recurrence of 10 to 12 months[6,7]. About half of these patients (51%) are diagnosed with isolated distant systemic recurrence. This affects liver, bone and lung mainly[5-7]. Locoregional recurrence or a combination of locoregional and distant recurrence occur less frequent (14% and 35%, respectively)[7]. After diagnosing recurrent esophageal cancer poor median survival rates of 3 to 8 months have been reported[8].

Currently, most institutes use conventional imaging modalities such as computed tomography (CT) and endoscopy with or without endoscopic ultrasound (EUS) for the detection of recurrent esophageal cancer. However, the interpretation of these imaging techniques after prior treatment is difficult due to local anatomic changes caused by surgery[9]. In addition, distant recurrent esophageal cancer may be radiological occult on CT or may occur in unusual and unexpected locations outside the conventional field coverage of CT[10].

Whole-body ^{18}F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and integrated ^{18}F-FDG PET/CT have emerged as useful adjuncts to conventional staging modalities in the pre-treatment staging of esophageal cancer. In particular, baseline ^{18}F-FDG PET/CT has gained ground by outperforming CT alone in the detection of unexpected distant metastases[11]. Accordingly, ^{18}F-FDG PET or PET/CT may also be a very useful method for detecting recurrent disease in the post-operative follow-up of esophageal cancer patients as recurrences predominantly tend to occur at distant sites[7]. In the past years, several studies have been published on the utility of ^{18}F-FDG PET or PET/CT in the detection of esophageal cancer recurrence. However, it is difficult to draw conclusions based on the individual studies because methodological quality may vary, sample sizes are generally small and differences in study design and patient populations may cause heterogeneity in reported outcomes.

In order to critically appraise and potentially overcome shortcomings of individual studies the aim of this study was to systematically review and meta-analyze the diagnostic performance of ^{18}F-FDG PET and PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent.

METHODS

The study protocol has been registered in the PROSPERO international prospective register of systematic reviews and accessible at http://www.crd.york.ac.uk/prospero/ (Registration number: CRD42014009615).

Search strategy

On the 16th of December 2014 a systematic search was performed in the databases Medline (via Pubmed), Embase and the Cochrane library. The full search strategy is presented in Table 1.

Study selection

After removing duplicates of the retrieved articles, titles and abstracts were screened for eligibility by two authors independently (L.G. and P.S.N.v.R.). The full text of potentially relevant articles was retrieved and independently assessed by two authors for inclusion (L.G. and P.S.N.v.R.).

Studies examining the test accuracy of ^{18}F-FDG PET or integrated ^{18}F-FDG PET/CT, in either routine clinical follow-up with a fixed time interval irrespective of physical complaints, or in symptomatic patients suspected of recurrent esophageal cancer were deemed eligible for inclusion. Only studies that included patients who were previously treated with curative intent for esophageal cancer, and that reported on the diagnostic accuracy of ^{18}F-FDG PET or PET/CT for the detection of disease recurrence were included. Treatment with curative intent should have had at least included surgery, either or not combined with (neo)adjuvant chemo(radio)therapy. The reference standard was recurrent esophageal cancer as confirmed by histopathological biopsy or clinical follow-up.

Case reports, studies with less than 10 included patients, reviews, poster abstracts and animal studies were excluded. Also publications written in another language than Dutch, English or German were excluded from this review. Missing data of possible eligible studies were requested from study authors. References of the included studies and of related review studies were also screened for inclusion. Disagreements regarding the eligibility of a study were resolved by consensus.

Data extraction and quality assessment

Study and patient characteristics along with ^{18}F-FDG PET or PET/CT parameters were extracted from each study. The quality of the included studies was critically appraised by two authors independently (L.G. and P.S.N.v.R.), according to the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[12]. QUADAS-2 assesses risk of bias and

applicability concerns on four key domains including, patient selection, index text, reference standard and flow and timing, respectively. To reach a judgment on the risk of bias the provided signaling questions of the QUADAS-2 tool were used. Risk of bias and applicability concerns were judged as 'low', 'high', or 'unclear' risk or concern for the various QUADAS domains.

Statistical analysis

The target condition consisted of the presence of recurrent esophageal cancer as determined by histopathological biopsy or clinical follow-up. From each included study the number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) were obtained on a 'per-patient' basis if available. From studies reporting on a 'per-lesion' or 'per-scan' basis the reported sensitivities and specificities were used, but the absolute numbers leading to these estimates according to the total number of patients with and without recurrent disease were recalculated to prevent overestimation of the weight of the results. Subsequently, for each study the sensitivity and specificity along with 95% confidence intervals (95% CIs) were calculated and depicted in Forest plots.

A bivariate random effects model was used to obtain pooled estimates of sensitivity and specificity with their corresponding 95% CIs from the individual studies. The bivariate model uses a random effects approach to incorporate heterogeneity beyond chance as a result of clinical and methodological differences between studies[13]. The bivariate model also estimates whether sensitivities and specificities are (negatively) correlated across studies due to implicit differences in threshold to consider a ^{18}F-FDG PET or PET/CT scan suspected for recurrence (positive index test result). The pooled estimate of sensitivity and specificity and the corresponding 95% confidence ellipse is shown in ROC space[14].

Subgroup analyses were performed by adding the following study characteristics (covariates) to the bivariate model: 'standalone ^{18}F-FDG PET' versus 'integrated ^{18}F-FDG PET/CT', 'index test performed on indication' versus 'index test performed as part of routine follow-up', and 'Asian studies' versus 'non-Asian studies'. A p-value of <0.05 was considered statistically significant. The non-linear mixed model procedure of SAS (version 9.2, SAS Institute, Cary, N.C., USA) was used to estimate the parameters of the bivariate model.

RESULTS

Eligible Studies

The systematic search yielded 948 articles from Medline, 1684 from Embase and 60 from the Cochrane library (Table 1). After removing duplicates, 1867 articles remained of which

title and abstract were reviewed. Forty-three articles were deemed potentially relevant for this study. After reading the full text of the remaining studies, 35 articles were excluded because these concerned review studies (n=13), non-diagnostic studies (n=8), poster abstracts (n=5), publications in other than pre-specified languages (n=4), case reports (n=2), a study that included less than 10 patients (n=1) or studies in which insufficient data was available (n=2). Missing data of these latter two studies were requested from study authors without satisfying result[15,16]. Screening of references of these eligible articles and related review studies did not yield additional relevant publications. Consequently, eight studies met our inclusion and exclusion criteria comprising a total of 486 patients with esophageal cancer that underwent ^{18}F-FDG PET or PET/CT after previous treatment with curative intent. The described process of study selection is summarized in Figure 1.

The general characteristics of the included studies are presented in Table 2[17-24]. Table 3 outlines the used ^{18}F-FDG PET or PET/CT parameters and reference standards. Only one of the 8 studies was prospectively designed to answer this research question[22]. The duration of clinical follow-up after acquisition of a ^{18}F-FDG PET or PET/CT scan was less than 6 months in one of the included studies [23], at least 6 months or longer in five studies[17,18,20,21,24], and not described in two other studies[19,22]. In four studies the diagnostic value of integrated ^{18}F-FDG PET/CT was analyzed[17,18,20,21] and three studies analyzed the diagnostic value of standalone ^{18}F-FDG PET[22-24]. In one study the value of integrated ^{18}F-FDG PET with CT versus ^{18}F-FDG PET alone was analyzed separately; hereafter the data from this study is referred to as 'Roedl [1] ' and 'Roedl [2] ', respectively [19]. In four studies the diagnostic test was performed on routine basis[19,21-23], whereas in the other studies the diagnostic test was performed on indication during clinical follow-up[17,18,20,24]. In six studies ^{18}F-FDG-PET or PET/CT positive results were analyzed on a 'per-patient' basis, whereas in two studies the results were either assessed on a 'per-scan'[17] or 'per-lesion'[24] basis.

Quality assessment

The results of the quality assessment using the QUADAS-2 tool are presented in Table 4. The risk of bias concerning patient selection was low in 7 of the included studies; one study deemed at high risk of bias because it did not include a consecutive sample of patients[20]. Risk of bias with regard to the index test was low in all studies since the index test results were consistently interpreted without knowledge of the outcome of the reference test. However, the risk of bias for the reference test was deemed unclear for most studies because these articles lack to report whether or not the reference standard was interpreted without knowledge of the index test result. Furthermore, applicability concerns for patient selection were found in 4

studies because the study population consisted of patients that underwent a variety of treatment regimens. In general, there were only few high concerns with regard to the risk of bias and applicability, the quality of the currently available literature was considered reasonable.

Diagnostic accuracy

The results of two studies that assessed the diagnostic value of ^{18}F-FDG PET or PET/CT on a 'per-lesion' or 'per-scan' basis were adjusted according to their sample size[17,24]. The paired Forest plots of sensitivity and specificity of the eight individual studies are presented in Figure 2. The reported sensitivities ranged from 89% to 100% and specificities from 55% to 94%. For the calculation of the overall pooled estimates only the data of Roedl [1] - and not of Roedl [2] - was used to prevent using the data from this study twice[19]. Sensitivity was eventually pooled with a fixed effect model as the between-study variation was not larger than could be expected by chance. More variation than expected by chance was observed for specificity, therefore a random effects pooling was used for specificity. Pooled estimates of sensitivity and specificity were 96% (95% CI: 93% to 97%) and 78% (95% CI: 66% to 86%), respectively. The estimates from the individual studies, and the pooled estimates of sensitivity and specificity together with the 95% confidence ellipse are shown in Figure 3.

The planned subgroup analysis was restricted to specificity alone as there was no real heterogeneity in sensitivity. These subgroup analysis revealed no statistically significant difference in specificity according to type of PET-scanner (standalone PET versus integrated PET/CT), indication of scanning (part of routine follow-up versus on indication), and country of origin (Asian versus non-Asian) (Table 5).

TABLE 1. Full text of search strategy and results as on 16 December 2014

No.	Search query	Pubmed	Embase	Cochrane
1	pet OR pet-ct OR fluorodeoxyglucose OR "2 fluoro 2 deoxy" OR FDG OR positron emission tomography OR positron-emission tomography OR "18fdg"	73.205	94.057	3.121
2	esophageal OR esophagus OR oesophageal OR oesophagus OR gastro- esophageal OR gastro-oesophageal OR gastro-esophageal OR oesophagogastric OR esophagogastric	128.173	127.316	8.707
3	cancer OR cancers OR tumor OR tumour OR tumors OR tumours OR neoplasm OR neoplasms OR malignancy OR malignancies OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas	2.206.283	2.270.954	90.252
4	**#1 AND #2 AND #3**	**948**	**1.684**	**60**

TABLE 2. Characteristics of the 8 included studies

First author, year	Country	Type of study	No. of patients	Mean age (range)	Gender (M/F)	Histology (SCC/ AC/ other)	Initial treatment	Type of scanner, slice thickness of CT, acquisition mode and reconstruction method	Reason for imaging
Sharma, 2014	India	Retro	180	56 (26-81)	126/54	115/59/6	S, C, SC, CR, SR, nCRT and S	Integrated PET/CT, 4mm, 3D, IR	On indication
Sun, 2009	China	Retro	20	55 (39-68)	15/5	NR	S and adj R	Integrated PET/CT, 3.3mm, IR, NR	On indication
Roedl, 2008	USA	Retro	47	NR (NR)	35/12	11/36/0	S, R	Standalone PET and integrated PET/CT, 2mm, NR, NR	Routine
Guo, 2007	China	Retro	56	NR (38-77)	47/9	NR	nCRT and S	Integrated PET/CT, 4.24mm, NR, IR	On indication
Jadvar, 2006	USA	Retro	46	NR (47-84)	50/10	NR	S, SC, R, C, SCR	Integrated PET/CT, 3.4mm, NR, IR	Routine
Teyton, 2008	France	Prosp	41	59 (43-83)	38/3	31/10/0	S, SC	Standalone PET, NR, 3D, IR	Routine
Kato, 2004	Japan	Retro	55	61 (36-74)	48/7	50/3/2	S	Standalone PET, 3.1mm, NR, IR	Routine
Flamen, 2000	Belgium	Retro	41	62 (NR)	36/5	14/27	S	Standalone PET, NR, NR, IR	On indication

Retro=retrospective; Prosp=prospective; SCC=squamous cell carcinoma; AC=adenocarcinoma; S=surgery; C=chemotherapy; SC=surgery and chemotherapy; CR=chemoradiotherapy; SR=surgery and radiotherapy; R=radiotherapy; adj=adjuvant; nCRT=neoadjuvant chemoradiotherapy;3D=three dimensional; 2D=two dimensional; IR=iterative reconstruction; NR=not reported.

TABLE 3. ^{18}F-FDG PET or PET/CT parameters, methods of image interpretation, and reference standard of included studies

First author, year	FDG dose	Time between FDG administration and scanning (min)	Criteria for positive scan	Interpreters	Reference standard	Duration of clinical follow-up	Patients with recurrence (%)
Sharma, 2014	370 MBq	45-60	-Suspicious CT lesions with FDG uptake -Suspicious CT lung lesion -FDG hotspot liver	Two nuclear medicine physicians	Histology and/or clinical follow-up with imaging	Minimally 6 months	NR
Sun, 2009	60 MBq	60	Markedly to moderately increased uptake of FDG	Two nuclear medicine physicians	Histology and/or clinical follow-up	Minimally 10 months	55.0
Roedl, 2008	555 MBq	60	Focal and eccentric uptake of FDG	Nuclear medicine physicians and radiologists.	Histology and/or clinical follow-up with imaging	NR	57.4
Guo, 2007	370 MBq	60	Focal uptake of FDG	Three nuclear medical physicians	Histology and/or clinical follow-up with imaging	Minimally 6 months	80.4
Jadvar, 2006	555 MBq	60	Focal uptake of FDG	NR	Histology and/or clinical follow-up with imaging	Up to 18 months	60.9
Teyton, 2008	355 MBq	60	Focal uptake of FDG	Two nuclear medicine physicians	Histology and/or clinical follow-up with imaging	NR	56.1
Kato, 2004	275-370 MBq	40	NR	Two nuclear medicine physicians	Histology and/or clinical follow-up with imaging	Within 6 months	49.1
Flamen, 2000	6.5MBq/kgmaximum 555 MBq	60	NR	Two nuclear medicine physicians	Histology and/or clinical follow-up with imaging	Minimally 6 months	80.5

NR=not reported.

TABLE 4. Quality assessment of included studies

First author, year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Sharma, 2014	L	L	U	L	H	L	L
Sun, 2009	L	L	U	L	H	L	L
Roedl, 2008	L	L	U	U	L	L	L
Guo, 2007	H	L	U	L	H	L	L
Jadvar, 2006	U	L	H	U	H	L	L
Teyton, 2008	L	L	U	U	L	L	L
Kato, 2004	L	L	U	H	L	L	L
Flamen, 2000	L	L	U	L	L	L	L

H=high; L=low; U= unclear.

TABLE 5. Results from the subgroup analyses for specificity

Factor	No. of studies	Specificity (95% CI)	p-value
Type of scan			
^{18}F-FDG PET/CT	5	78% (70 - 85)	0.213
^{18}F-FDG PET	4	70% (59 - 80)	
Indication of test			
Routine imaging	4	78% (69 - 86)	0.748
Clinical suspicion	4	76% (65 - 85)	
Country of origin			
Asian	4	73% (64 - 81)	0.099
Non-Asian	4	84% (73 - 91)	

Subgroup analysis was only performed for specificity, because there was no variation beyond chance for sensitivity.

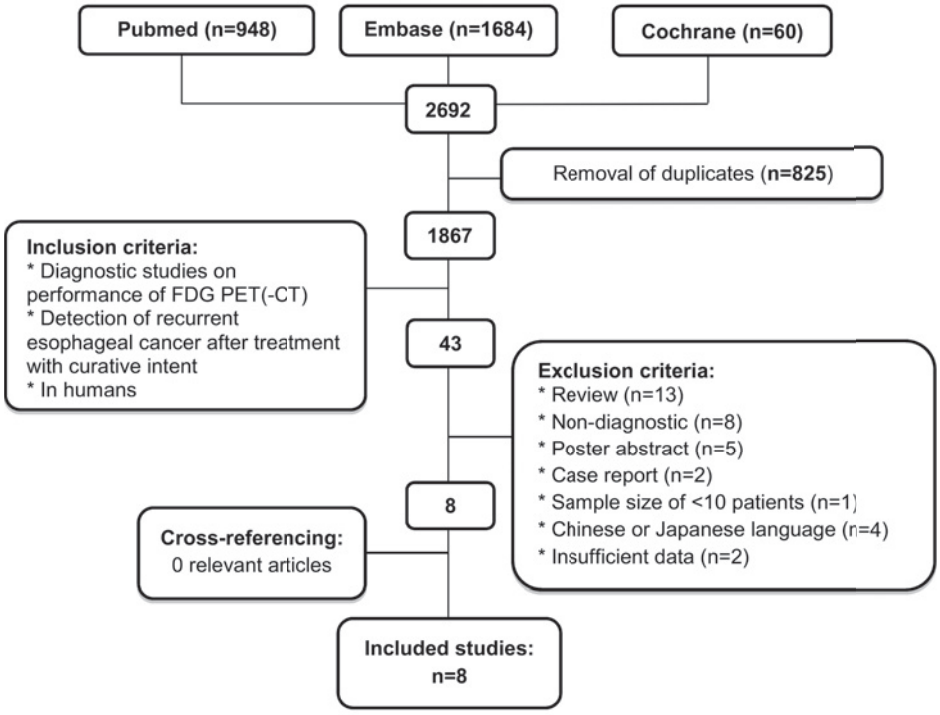

Figure 1. Flowchart summarizing search results and study selection.

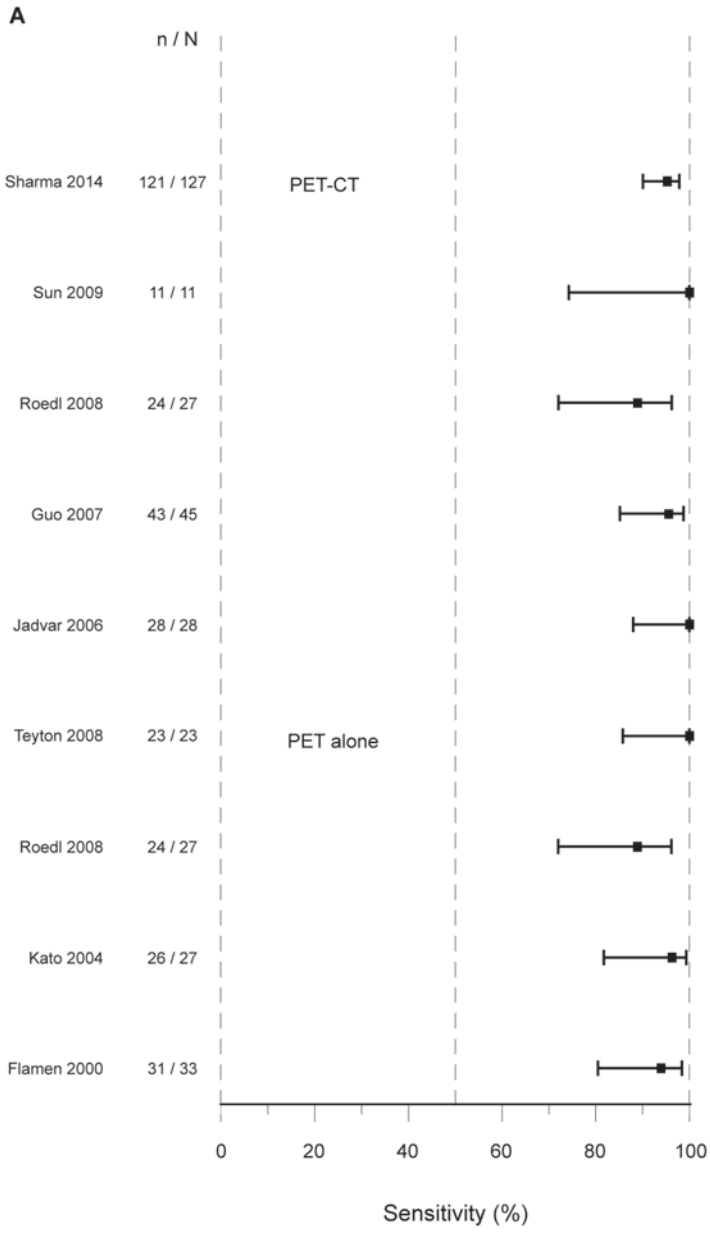

Figure 2. A: Forest plot of sensitivity of integrated ^{18}-F-FDG PET/CT and PET alone for the detection of recurrent esophageal cancer after treatment with curative intent. n = number of TP; N = number of TP + number of FN.

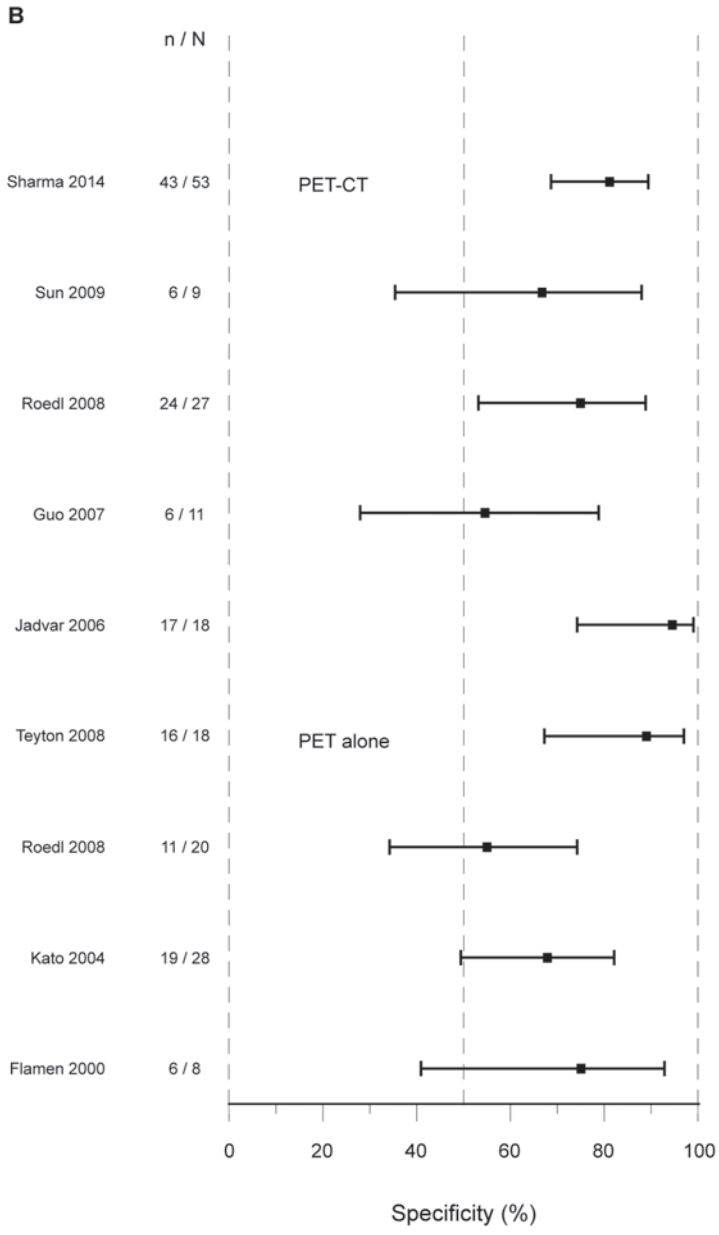

Figure 2. B: Forest plot of specificity of ^{18}F-FDG PET with integrated CT and PET alone for the detection of recurrent esophageal cancer after treatment with curative intent. n = Number of TN; N = number of TN + number of FP.

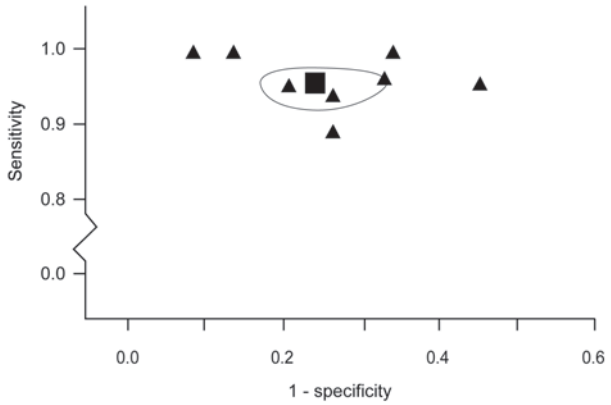

Figure 3. Pooled estimate of sensitivity and specificity (square) and corresponding 95% confidence ellipse along with the estimates from the individual studies (triangles) in ROC space.

DISCUSSION

This study is the first study to systematically review and summarize the currently available evidence on the accuracy of ^{18}F-FDG PET and PET/CT for diagnosing recurrent esophageal cancer after primary treatment with curative intent. The methodological quality of the eight included studies analyzed by the QUADAS-2 tool concerning risk of bias was low in most studies. Pooled estimates for ^{18}F-FDG PET and PET/CT yielded a high sensitivity and moderate specificity of 96% and 78% respectively. Sensitivity was consistently high in all studies, but variation was present in specificity. Subgroup analysis could not link specific study characteristics to systematically higher or lower specificity. Current evidence indicates that ^{18}F-FDG PET and PET/CT are valuable tests for clinical practice in the follow-up of patients with esophageal cancer after primary treatment.

Certain limitations apply to this meta-analysis. Methodological concerns that may have influenced the results of the various studies include absence of blinding the index test from the reference test, and inclusion of heterogeneous treatment modalities among individual studies. Another limitation is the limited number of included studies in this meta-analysis. Also, in this meta-analysis three of eight studies only included patients with a clinical suspicion of recurrence. This may have led to an overestimation of the diagnostic value of ^{18}F-FDG PET or PET/CT, as these patients have an increased pre-test probability compared to patients without suspicion of recurrence. However, subgroup analysis could not confirm this potential difference in diagnostic accuracy of ^{18}F-FDG PET or PET/CT on clinical indication or as part

of routine follow-up (specificity 78% [95% CI: 69% to 86%] versus 76% [95% CI: 65% to 85%], respectively; p=0.748). In addition, the country of origin did not seem to have influenced the results of the different studies significantly. Last, differential verification bias was of concern in most included studies as different reference standards were used for confirmation of the diagnosis. Most negative ^{18}F-FDG PET or PET/CT cases were verified by a potentially less reliable and second best reference test (clinical follow-up instead of histopathological biopsy), which may have resulted in a slight overestimation of sensitivity and underestimation of specificity[25]. None of the included studies applied a correction method to their results for this potential bias.

Conventional imaging modalities for recurrent esophageal cancer include, endoscopy with or without EUS and CT of thorax and abdomen. EUS has proven to be effective for the detection of locoregional recurrence (sensitivity > 90%), but both endoscopy and EUS fail to detect distant metastases[26]. Currently, distant metastases are of particular interest since the incidence of locoregional recurrence is substantially reduced by new treatment algorithms, including neoadjuvant chemo(radio)therapy[7]. CT scans are commonly used for detection of distant metastases, although the diagnostic value of CT for local recurrence is limited at the site of resection due to anatomic distortion caused by surgery and radiotherapy[9]. Furthermore, only limited data on the diagnostic value of CT for detecting recurrent esophageal cancer is available with reported sensitivities ranging from 65% to 89%[22,23]. The pooled sensitivity estimate for ^{18}F-FDG PET and PET/CT of 96% from this meta-analysis indicates that ^{18}F-FDG PET and PET/CT is likely to outperform CT to this regard, which is confirmed by direct comparison in two studies[22,23].

Comparison of reported specificities for CT and the current pooled specificity estimate for ^{18}F-FDG PET and PET/CT suggests an inferior specificity for ^{18}F-FDG PET and PET/CT compared to standalone CT (78% versus 79%-91%, respectively)[22,23]. The lower specificity of ^{18}F-FDG PET is a common problem in oncologic patients and is mainly caused by false positive findings due to chronic inflammation after surgery, chronic respiratory tract disease, radiation pneumonitis or dilation of anastomotic strictures[20,27,28]. A combination of metabolic imaging (^{18}F-FDG PET) with anatomic imaging (CT) has been reported to improve diagnostic accuracy compared to PET alone, especially in diagnosing locoregional recurrence[15,17,19]. To this regard, the only direct comparative study in esophageal cancer recurrence diagnosis found a higher specificity in favor of PET/CT compared to PET alone (75% versus 55%, respectively)[19]. However, this potential benefit of ^{18}F-FDG PET/CT as opposed to standalone ^{18}F-FDG PET for diagnosing recurrent esophageal cancer did not reach statistical significance by subgroup

analysis in this meta-analysis (specificity 78% [95% CI: 70% to 85%] versus 70% [95% CI: 59% to 80%], respectively; p=0.213).

The specificities used in this meta-analysis were derived from analysis on a per-patient basis and the pooled results can therefore not exclude the possibility of superiority of ^{18}F-FDG PET/CT over PET for specific anatomic sites. Anatomic site-specific TP and FP numbers were reported on a per-lesion basis in 5 of 8 studies[17,19,20,23,24] and suggested a difference in the positive predictive values (e.g. TP / [TP + FP]) for diagnosing locoregional recurrence using ^{18}F-FDG PET/CT (range 79%-95%) [17, 19, 20] compared with ^{18}F-FDG PET (range 59%-68%)[19,23,24]. The differences between positive predictive values for diagnosing distant recurrence of PET/CT (range 89%-95%)[17,19,20] and PET (84%-90%) studies were minor[19,23,24]. However, in contrast to specificities, the pooling of positive predictive values is questionable due to their strong dependency on the pre-test probability (e.g. prevalence of true recurrences), which varies among the included studies with different clinical settings. To this regard, another subject of note is the continuous technological progress of ^{18}F-FDG PET/CT image generation and reconstruction algorithms, and ^{18}F-FDG PET with integrated magnetic resonance imaging (MRI) is now clinically introduced[29]. These developments may prove to further increase the accuracy in diagnosing recurrent esophageal cancer.

In the current guidelines of the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) there is no room for routine imaging or endoscopy with biopsies after initial treatment for esophageal cancer[30,31]. The key reason to refrain from routine imaging is the limited amount of adequate therapeutic options when recurrence is detected. Current treatment options for recurrent disease consist of salvage chemo(radio)therapy which is associated with symptomatic relief and improved survival rates[32,33]. Furthermore, recent experimental studies have demonstrated that re-operation for selected cases of localized recurrence or solitary recurrence in lymph nodes, lungs and subcutaneous lesions is safe and may improve survival[34-38]. This is supported by a recent study that demonstrated a significant survival benefit for patients treated with salvage lymphadenectomy compared to chemo(radio)therapy in patients with cervical lymph node recurrence[37].

Future clinical decision-making with regard to treatment strategy for recurrent disease will depend on the extent and location of the recurrence. Routine imaging with CT and PET has been shown to possess the ability to detect recurrent esophageal cancer in a pre-symptomatic phase[39,40]. However, so far no studies combining routine imaging with aggressive treatment

strategies are available. Also, very little is known about cost-effectiveness of routine imaging and gain of quality of life after early detection of recurrent esophageal disease. Therefore, with the limited evidence available for routine imaging in recurrent esophageal cancer, at this moment routine imaging is not recommended. In case recurrent disease is clinically suspected, the method of choice is ^{18}F-FDG PET/CT.

This meta-analysis demonstrates that ^{18}F-FDG PET and PET/CT are reliable imaging modalities with a high sensitivity and moderate specificity for detecting recurrent esophageal cancer. The use of ^{18}F-FDG PET or PET/CT particularly allows for a minimal false negative rate. However, histopathological confirmation of ^{18}F-FDG PET and PET/CT suspected lesions remains required, since a considerable false positive rate is noticed. The benefit of ^{18}F-FDG PET and PET/CT over conventional imaging techniques, in terms of cost-effectiveness and improving clinical outcome, remains subject of debate. Future studies are warranted to analyze whether earlier detection of recurrent esophageal cancer along with more aggressive therapeutic approaches will improve survival and quality of life.

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6

Preoperative nomogram to predict early disease recurrence after neoadjuvant chemoradiotherapy and surgery for esophageal adenocarcinoma

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ABSTRACT

Objective

To develop a nomogram that estimates 1-year recurrence free survival (RFS) after trimodality therapy for esophageal adenocarcinoma, and assess the overall survival (OS) benefit of esophagectomy after chemoradiotherapy (CRT) on the basis of 1-year recurrence risk.

Methods

In total 568 consecutive patients with potentially resectable esophageal adenocarcinoma who underwent CRT were included for analysis, including 373 patients who underwent esophagectomy after CRT (trimodality therapy), and 195 who did not underwent surgery (bimodality therapy). A nomogram for 1-year RFS was created using a Cox regression model. The upper tertile of the nomogram score was used to stratify patients in low-risk and high-risk groups for 1-year recurrence. The 5-year OS was compared between trimodality and bimodality therapy in low-risk and high-risk patients after propensity score matching, respectively.

Results

Median follow up for the entire cohort was 62 months. The 5-year OS in the trimodality and bimodality treatment groups was 56.3% (95% confidence interval [CI]: 47.9-64.7) and 36.9% (95% CI: 31.4-42.4), respectively. The final nomogram for the prediction of 1-year RFS included male gender, poor histologic grade, signet ring cell adenocarcinoma, cN1, cN2-3, and baseline SUV_{max}, with accurate calibration and reasonable discrimination (C-statistic: 0.66). Trimodality therapy was associated with improved 5-year OS in low-risk patients (p=0.003), whereas it showed no significant survival benefit in high-risk patients (p=0.302).

Conclusion

The proposed nomogram estimates early recurrence risk. The addition of surgery to CRT provides a clear OS benefit in low-risk patients. The OS benefit of surgery in high-risk patients is less pronounced.

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) combined with surgical resection of the esophagus (trimodality therapy) is a generally recommended treatment strategy with curative intent for patients with locally advanced esophageal cancer[1,2]. Definitive CRT (bimodality therapy) is an alternative approach for patients with a poor performance status or inoperable locally advanced esophageal cancer[3,4]. Despite recent improvement in multimodality treatment and perioperative care, esophageal cancer remains a devastating condition for the patient with an estimated 5-year overall survival (OS) rate of 36-47% after trimodality therapy[5–7].

The relatively poor OS even after trimodality therapy is partially attributable to the high incidence (49-85%) of disease recurrence after surgery[8]. The remaining OS of patients in this setting is generally poor[9]. In order to advocate an extensive surgical resection such as esophagectomy, there should be a fair chance of improving OS combined with an acceptable health-related quality of life[10]. Despite improvements in (minimally invasive) surgical techniques, esophageal resection can still induce significant treatment-related morbidity and mortality[11,12]. Furthermore, esophagectomy has been associated with a reduction in health-related quality of life up to 3-12 months following surgery[13–15]. As such, in the group of patients who experience early disease recurrence within 1-year of completing their treatment the benefit of surgery would probably not outweigh its potential side-effects[13–15]. Some suggest that consideration should therefore be given to less invasive treatment strategies in patients who are likely to have early disease recurrence after surgery[10]. Preoperative identification of these patients may help to guide subsequent treatment decision-making.

Currently most available studies assessing prognosis after trimodality therapy rely on the postoperative available pathology results of the resection specimen, limiting their practical use at the time of surgical decision-making[10,16,17]. Additionally, no single clinicopathological characteristic in esophageal cancer can yet optimally predict prognosis preoperatively. Therefore, the aim of the current study was to develop a preoperative risk prediction model for 1-year recurrence free survival (RFS) after trimodality therapy for esophageal adenocarcinoma – incorporating multiple clinicopathological characteristics and ^{18}F-FDG PET/CT features – and assess the OS benefit of subsequent surgery after CRT in patients low and high at risk of early disease recurrence.

METHODS

Study population

From a prospectively acquired database, all patients with locally advanced potentially resectable adenocarcinoma of the esophagus (cT1N+ or cT2-4aN_{any}) considered eligible for curative resection after initial staging who underwent trimodality therapy or bimodality therapy between January 2006 and February 2016, at the MD Anderson Cancer Center were identified. Patients were excluded if ^{18}FDG-PET/CT scanning before and after CRT was not performed, or if restaging after CRT discovered distant metastases. Staging was performed in accordance with the 7th edition of the International Union Against Cancer cTNM-classification[18]. Initial diagnostic work-up included endoscopy with biopsy, endoscopic ultrasound (including fine-needle aspiration if indicated), and ^{18}F-FDG PET/CT. The cT-status and cN-status reported in this study were determined before the start of CRT. This study was approved by the institutional review board at MD Anderson Cancer Center and the requirement to obtain informed consent was waived. The data were analysed in May 2017.

Treatment protocol

CRT consisted of fluoropyrimidine (intravenous or oral) with either a platinum or a taxane compound with concurrent radiotherapy (45 or 50.4 Gy in fractions of 1.8 Gy) (Table 1). Patients were considered to have received trimodality therapy if esophagectomy was performed within 4 months after completion of CRT. Reasons to refrain from surgery (bimodality therapy) included patient and physician choice (e.g. physician preference for observation), or a decline in performance status secondary to CRT. Surgical treatment consisted of either transhiatal esophagectomy with abdominal lymphadenectomy or Ivor Lewis esophagectomy with abdominal and thoracic lymphadenectomy. The choice of technique was at the discretion of the treating surgeon.

Follow-up

After treatment patients were routinely monitored at intervals of 3 months in the first year, 6 months during the second and third year, and 12 months until 5 years after treatment or until death. The follow-up assessment consisted of routine blood tests, chest/abdominal CT, endoscopy with biopsies, and/or ^{18}F-FDG PET/CT. The main endpoint of this study was 1-year RFS after trimodality therapy and was calculated from the day of surgery to either the date of recurrence or end of follow-up (censored at 12 months in case of >12 months follow-up). OSwas calculated from the end of CRT to either date of death or last follow-up (censored at 5 years in case of >5-year follow-up).

Preoperative predictors

Clinical characteristics were derived from the prospective collected departmental registry. Initial selection of predictors for for 1-year RFS were pre-specified based on previous literature to prevent overfitting of the model. Categories were based on previously published cut-off points (Table 1)[10,19–21].

Statistical analysis

Missing data were considered at random and handled using imputation with the iterative Markov chain Monte Carlo method[22]. Kaplan-Meier curves were used to assess RFS and OS, and differences were evaluated using the log-rank test. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt', 'optmatch', 'rms', 'Hmisc', 'mice', packages). A *p*-value of <0.05 was considered statistically significant.

Model development

For the development of the model for 1-year RFS only trimodality patients were used. In case of high correlated variables (i.e. Spearman rank correlation coefficient $r \geq 0.6$) the easiest measurable factor was included. The initial multivariable Cox regression model was reduced by using backward stepwise elimination and the Akaike Information Criteria (AIC) was used to compare different models. The discriminative ability of the final model for 1-year RFS was evaluated using Harrell's C-statistic[23]. For internal validation the model was subjected to 200 bootstrap resamples to calculate the optimism of the model, after which the C-statistic was adjusted and a shrinkage factor calculated to correct the β-coefficients. Calibration of the final model, which reflects the agreement between predicted versus actual (observed) outcomes, was visualized with calibration plots after bias correction. The final model was used to construct a nomogram.

Propensity score matching

The upper tertile of the nomogram score was used to stratify patients in low-risk and high-risk groups for recurrence within 1-year. Propensity score matching was used to balance patient characteristics between the trimodality and bimodality group within the different risk strata. A propensity score was generated using logistic regression, based on all covariates presented in Table 2. Subsequently, the 'nearest-neighbour' matching technique was used to generate matched pairs of cases (1:1) using a caliper width of 0.45[24]. Kaplan-Meier curves were used to compare OS between trimodality and bimodality for low-risk and high-risk groups, respectively.

RESULTS

Patient and treatment-related characteristics

From 568 patients with esophageal adenocarcinoma that met our inclusion and exclusion criteria, 373 underwent trimodality therapy and 195 underwent bimodality therapy (Figure 1). The distribution of patient and treatment-related characteristics are summarized in Table 1. Of the trimodality patients 345 (93%) underwent Ivor-Lewis esophagectomy, in 352 (94%) a R0 resection was achieved, and the median number of harvested lymph nodes was 21 (Interquartile range: 15-26). Most common postoperative complications were pulmonary complications (26%), atrial fibrillation (15%), and anastomotic leakage (9%). The median follow up was 62 months (range 1-130) for the entire cohort. The 5-year OS rate in the trimodality and bimodality treatment groups were 56.3% (95% confidence interval [CI]: 47.9-64.7) and 36.9% (95% CI: 31.4-42.4), respectively.

Preoperative prediction model for early disease recurrence

Among the 373 trimodality patients, 102 (Kaplan-Meier estimate: 28%) had recurrence within 1-year following esophagectomy, with 91 (89%) having distant metastases. Median OS after documentation of disease recurrence within 1-year after surgery was 9.1 months (95% CI: 6.6-11.6). A detailed description of the location and treatment of 1-year disease recurrence is summarized in Online Supplemental Table 1.

The association of clinical characteristics with 1-year RFS in univariable analysis are presented in Online Supplemental Table 2. After multivariable analysis, male gender (optimism adjusted hazard ratio [aHR]: 2.13, 95%CI: 0.95-4.77), poor tumor differentiation grade (aHR: 1.59, 95%CI: 1.07-2.35), signet ring cell adenocarcinoma (cHR: 1.72, 95% CI: 1.07-2.75), baseline cN1 (aHR: 1.72, 95%CI: 1.09-2.75), baseline cN2-3 (aHR: 2.07, 95%CI: 1.27-3.38), and baseline SUV_{max} ≥7 (aHR: 1.71, 95%CI: 1.09-2.69), were independently predictive for 1-year RFS, respectively (Online Supplemental Table 3). A nomogram based on these variables was constructed (Figure 2). The discriminative ability of the nomogram was reasonable with an apparent C-statistic of 0.67, and 0.66 after adjustment for optimism. Calibration was accurate, with predictions corresponding closely with the actual observed 1-year RFS probability (Online Supplemental Figure 1).

Risk stratification of early disease recurrence

Based on the nomogram score patients receiving trimodality treatment were grouped into a low-risk (<276 nomogram points; number of patients in group = 256) and a high-risk group (≥276 nomogram points; number of patients in group = 117) for early disease recurrence,

respectively. The corresponding 1-year RFS estimate of the low-risk group (80%) was significantly better than high-risk group (54%) (log-rank test: $p<0.001$). After applying the same nomogram score cut-off values to patients in the bimodality group, stratification into low-risk (number of patients in group = 135) and high-risk (number of patients in group = 60) groups allowed significant distinction between 1-year RFS (60% versus 46%, log-rank test: $p=0.049$, respectively).

Survival comparison between trimodality and bimodality therapy in low- and high-risk patients

After propensity score matching, balance in patient and tumor characteristics between the stratified trimodality and bimodality groups was achieved (Table 2). In the low-risk group 5-year OS was significantly better after trimodality therapy compared to bimodality therapy (66% vs. 46%, respectively; log-rank test: $p=0.003$). In the high-risk patients 5-year OS difference of trimodality versus bimodality therapy was not statistically significant (32% vs. 21%, respectively; log-rank test: $p=0.302$, respectively) (Figure 3).

TABLE 1. Patient, tumor, re-staging, and treatment-related characteristics of patients treated with trimodality or bimodality therapy

Characteristic	**Trimodality therapy (n= 373)**		**Bimodality therapy (n= 195)**		**p-value**	**Missing, n[d]**
Baseline staging	Value	%/SD	Value	%/SD		n (%)
Gender					0.229	0
Female	36	9.7%	13	6.7%		
Male	337	90.3%	182	93.3%		
Age (years)[a]	60	± 10	68	±9		0
BMI (kg/m^2)[a]	25.9	± 5.04	27.9	±6.04		0
ECOG performance status					<0.001	0
0	160	42.9%	49	25.1%		
1-2	213	57.1%	146	74.9%		
Weight loss					0.810	0
<10%	294	78.8%	152	77.9%		
≥10%	79	21.2%	43	22.1%		
Histologic grade					0.232	0
Good/Moderate	164	44.0%	96	49.2%		
Poor	209	56.0%	99	50.8%		
Signet ring cell adenocarcinoma					0.453	0
No	317	85.0%	161	82.6%		
Yes	56	15.0%	34	17.4%		

TABLE 1 (continued). Patient, tumor, re-staging, and treatment-related characteristics of patients treated with trimodality or bimodality therapy

Characteristic	**Trimodality therapy (n= 373)**		**Bimodality therapy (n= 195)**		**p-value**	**Missing, n[d]**
Baseline staging	Value	%/SD	Value	%/SD		n (%)
EUS-based tumor length (cm)					0.087	0
<4cm	150	40.2%	93	47.7%		
≥4cm	223	59.8%	102	52.3%		
Nontraversability by EUS					0.751	0
No	310	83.1%	160	82.1%		
Yes	63	16.9%	35	17.9%		
Clinical T status (seventh)[b]					0.920	0
IB/II	47	12.6%	24	12.3%		
III/IVa	326	87.4%	171	87.7%		
Clinical N status (seventh)[b]					0.111	0
cN0	133	35.7%	80	41.0%		
cN1	138	37.0%	77	39.5%		
cN2-3	102	27.3%	38	19.5%		
Maximum lymph node diameter[c]					0.676	0
<1cm	259	69.4%	139	71.2%		
≥1cm	114	30.6%	56	28.8%		
PET avid nodes at baseline					0.138	0
*m*N0	225	60.3%	130	66.7%		
*m*N+	148	39.7%	65	33.3%		
Celiac lymph node involvement					0.155	0
No	354	94.9%	190	97.4%		
Yes	19	5.1%	5	2.6%		
Induction chemotherapy					0.006	0
No	235	63.0%	145	74.4%		
Yes	138	37.0%	50	25.6%		
Chemotherapy regimen					<0.001	0
Oxaliplatin / 5-FU	150	40.2%	42	21.5%		
Docetaxel / 5-FU	104	27.9%	81	41.5%		
Docetaxel / Capecitabine	81	21.7%	44	22.6%		
Other	38	10.2%	28	14.4%		
Total Radiation dose (Gy)					0.192	0
45.0	17	4.6%	14	7.2%		
50.4	356	95.4%	181	92.8%		
Postchemoradiation staging						
Subjective assessment ^{18}F-FDG PET					0.001	0
No complete response	251	67.3%	103	52.8%		
Clinical complete response	122	32.7%	92	47.2%		

TABLE 1 (continued). Patient, tumor, re-staging, and treatment-related characteristics of patients treated with trimodality or bimodality therapy

Characteristic	**Trimodality therapy (n= 373)**		**Bimodality therapy (n= 195)**		**p-value**	**Missing, n[d]**
Postchemoradiation staging	Value	%/SD	Value	%/SD		n (%)
Postchemoradiation endoscopic biopsy					0.066	10 (1.7%)
No residual cancer	319	86.7%	174	91.6%		
Residual cancer	49	13.3%	16	8.4%		
Days from completion CRT to surgery[a]	60	± 19				0

Data are numbers, with percentages in parentheses. [a:] Expressed as mean ± SD; [b:]Classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[18]; [c:]Lymph node diameter was measured in the short axis by an experienced radiologists on the axial CT images; [d:]Number of missing values for each variable before imputation; ECOG: Eastern Cooperative Oncology Group; EUS: endoscopic ultrasonography.

TABLE 2. Patient, tumor, re-staging, and treatment-related characteristics of patients low- and high at risk of 1-year disease recurrence according to nomogram after propensity score matching

Characteristics	**Propensity score matched low-risk patients**					**Propensity score matched high-risk patients**				
	TMT (n= 118)		**BMT (n=118)**		**p-value**	**TMT (n= 54)**		**BMT (n=54)**		**p-value**
	value	%/SD	value	%/SD		value	%/SD	value	%/SD	
Gender (male)	108	91.5%	109	92.4%	0.811	52	96.3%	52	96.3%	0.497
Age (years)[a]	65	7	67	9	0.153	65	8	66	10	0.400
ECOG performance status (1-2)	71	60.2%	79	66.9%	0.279	41	75.9%	44	81.5%	0.481
Weight loss (≥10%)	22	18.6%	24	20.3%	0.742	15	27.8%	14	25.9%	0.828
Histologic grade (Poor)	35	29.7%	36	30.5%	0.887	54	100 %	54	100%	1.000
Signet ring cell adenocarcinoma (Yes)	7	5.9%	9	7.6%	0.156	16	29.6%	19	35.2%	0.537
EUS-based tumor length (≥4cm)	49	41.5%	52	44.1%	0.693	41	75.9%	41	75.9%	1.000
Nontraversability by EUS (Yes)	16	13.6%	22	18.6%	0.288	14	25.9%	10	18.5%	0.355
Clinical T status (III/IVa)[b]	95	80.5%	99	83.9%	0.496	53	98.1%	52	96.3%	0.558
Clinical N status (cN1)[b]	37	31.4%	35	29.7%	0.926	31	57.4%	33	61.1%	0.890
(cN2-3)	18	15.3%	17	14.4%		19	35.2%	18	33.3%	
FDG avid nodes at baseline (*m*N+)	31	26.3%	32	27.1%	0.883	30	55.6%	29	53.7%	0.847
Celiac lymph node involvement (Yes)	4	3.4%	1	0.8%	0.175	5	9.3%	4	7.4%	0.728
Baseline SUV_{max} (≥7)	64	54.2%	64	54.2%	1.000	53	98.1%	53	98.1%	1.000
Induction chemotherapy (Yes)	34	28.8%	33	28.0%	0.885	19	35.2%	16	29.6%	0.537

TABLE 2 (continued). Patient, tumor, re-staging, and treatment-related characteristics of patients low- and high at risk of 1-year disease recurrence according to nomogram after propensity score matching

Characteristics	Propensity score matched low-risk patients					Propensity score matched high-risk patients				
	TMT (n= 118)		BMT (n=118)		p-value	TMT (n= 54)		BMT (n=54)		p-value
	value	%/SD	value	%/SD		value	%/SD	value	%/SD	
Postchemoradiation staging										
Assessment ^{18}F-FDG PET (cCR)	49	41.5%	55	46.6%	0.431	17	31.5%	21	38.9%	0.420
Endoscopic biopsy (RC)	14	11.9%	11	9.3%	0.526	5	9.3%	5	9.3%	1.000

Data are numbers, with percentages in parentheses; [a]Expressed as mean ± SD; [b]Classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[18]; TMT: trimodality therapy; BMT: bimodality therapy; ECOG: Eastern Cooperative Oncology Group; EUS: endoscopic ultrasonography; SUV: standardized uptake value; cCR: clinical complete response; RC: residual cancer.

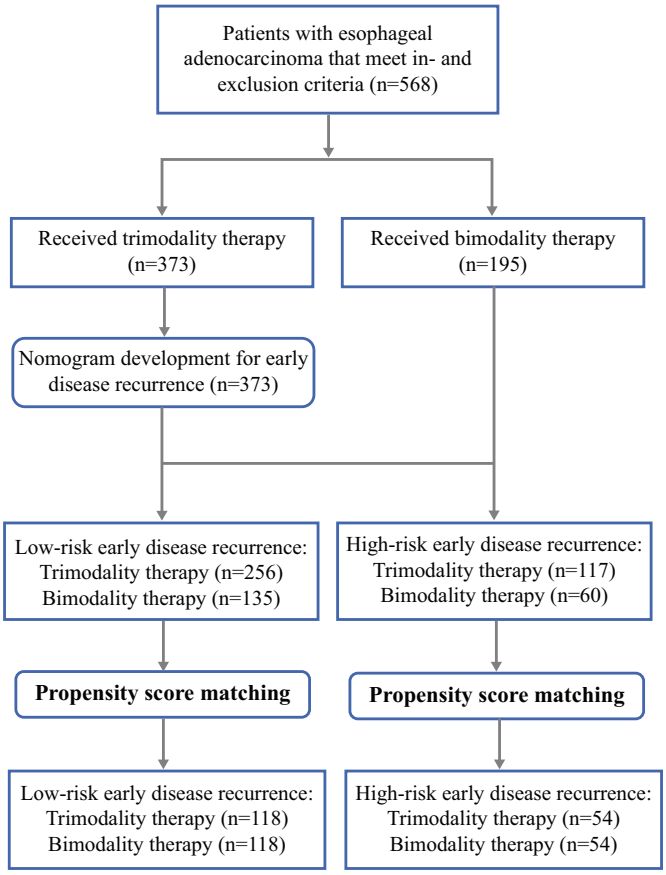

Figure 1: Flow diagram showing study profile.

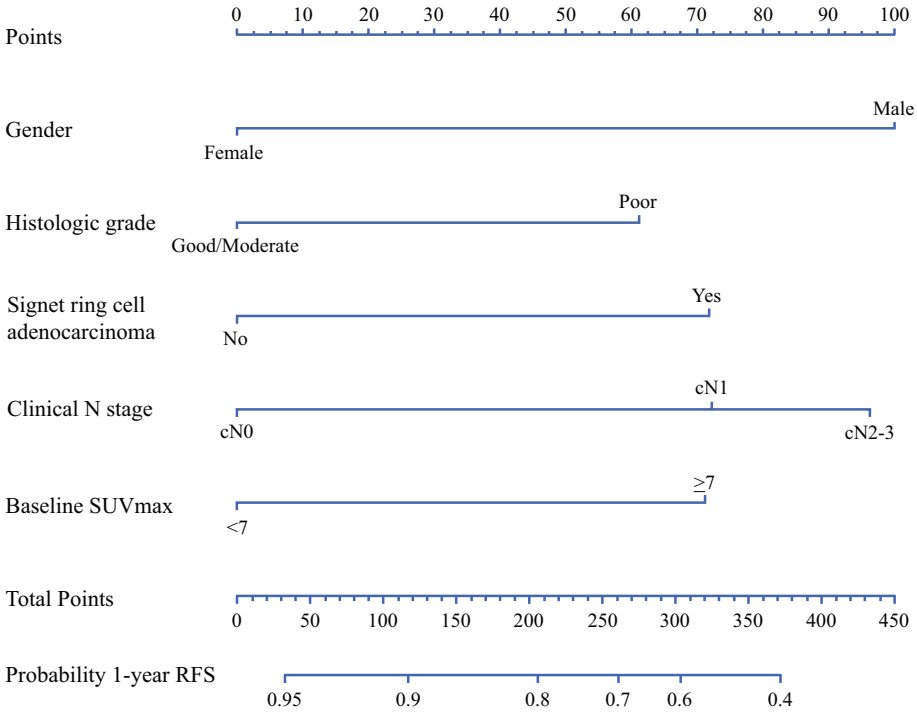

Figure 2: Nomogram for predicting 1-year recurrence free survival after trimodality therapy.

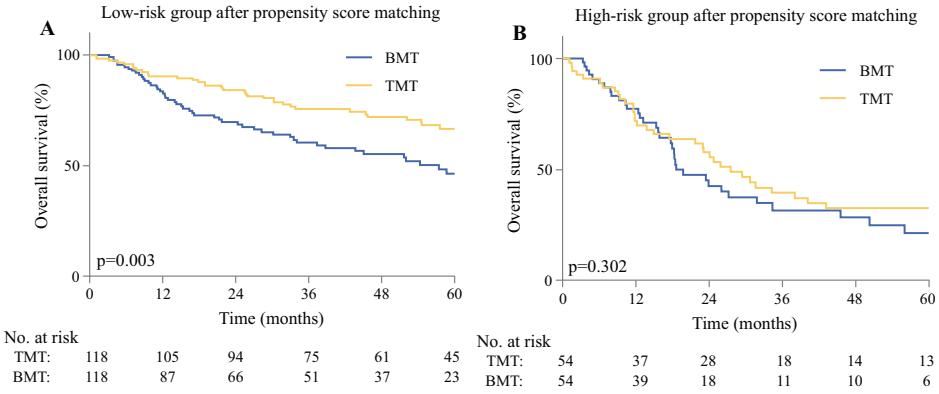

Figure 3: Comparison of overall survival between trimodality and bimodality treatment in the low-risk (**A**) and high-risk (**B**) groups after propensity score matching, respectively.

DISCUSSION

In this study a preoperative prediction model for early disease recurrence for esophageal cancer patients treated with trimodality therapy was developed. In summary, the proposed nomogram showed accurate calibration and reasonable discrimination (C-statistic: 0.66). Stratification into different risk groups based on the nomogram score allowed significant distinction between 1-year RFS and OS. Treatment with esophagectomy after CRT for patients with a low-risk of early disease recurrence resulted in a substantially higher 5-year OS compared to patients who underwent definitive CRT. Interestingly, the OS benefit of surgery was less apparent (and non-significant) in patients with a high-risk of early disease recurrence. Before surgery, by using this easy-to-use scoring system treating physicians could generate individualized predictions on early disease recurrence after surgery. As such, identifying subgroups of patients with different risks of early recurrence may impact shared treatment decision-making and choices of care.

Currently the NCCN guideline recommends preoperative chemoradiation with subsequent esophagectomy for medically fit patients with locally advanced esophageal cancer[2]. However, despite multimodality treatment strategies, studies have reported that as many as 29% of the patients experience disease recurrence within 1-year after esophagectomy[7]. The location of disease recurrence is typically systemic (86-88%) and results in a poor median OS of only 3-9 months[8,9,25]. These findings were verified by the current study in which 28% of the patients experienced disease recurrence within 1-year following trimodality therapy (89% systemic), with a median post-recurrence survival of 9 months.

The relatively high incidence of early disease recurrence after trimodality therapy suggests that small distant metastases, which are not detected by currently available staging techniques, may already have occurred at the time of esophagectomy[20]. Until clinical staging improves significantly, the key point of handling early disease recurrence is to identify high-risk patients and consider alternative treatment strategies. In case high-risk patients could accurately be identified, alternative less invasive strategies would be to delay esophagectomy after extensive CRT (with 50.4 Gy) and closely monitor patients for systemic disease. Salvage surgery could then still be an option in high-risk patients who did not develop early systemic recurrence within one year[26,27]. Another option would be to avoid chemoradiation due to its considerable morbidity and directly move to esophagectomy[28]. However, risk stratified treatment pathways in this setting that are most beneficial for patients have yet to be investigated.

The current study identified gender, poor tumor differentiation grade, signet ring cell adenocarcinoma, baseline cN1, cN2-3, and baseline SUV_{max} ≥7 as independent prognostic factors for 1-year RFS. These findings are in concordance with previous reports on risk factors for oncologic outcomes (i.e. RFS and OS) after esophagectomy[10,19–21,28]. By stratifying patients using cutoff values from the proposed nomogram, it was possible to separate patients in low-risk and high-risk groups for 1-year disease recurrence with distinct OS outcomes. For patients with a low-risk profile the prognosis after trimodality therapy was substantially better compared to patients treated with bimodality therapy.

In the high-risk group, however, patients had a 46% chance of disease recurrence within 1-year after surgery, with no significant OS difference compared to patients treated with bimodality therapy. Because the OS benefit of trimodality therapy in these high-risk patients was considerably less pronounced, an argument could therefore be made to refrain from surgery in these patients. Despite this, most physicians will find it difficult to withhold surgery from a patient with an otherwise resectable tumor based on the predicted outcomes of a nomogram. This is especially true when considering that even some of these high-risk patients are cured after trimodality therapy. Our nomogram should therefore be considered as a first step in the challenging process of patient selection. However, our study at least indicates that a subgroup of patients is likely not served by a multimodality treatment strategy. At best for now, these high-risk patients should be informed about their individual potential for disease recurrence in order for them to balance the possible risks and benefits of the various treatment strategies.

The discriminative ability of the proposed nomogram may benefit from further refinement with additional predictors in the future. The incorporation of validated risk prediction models for the occurrence and severity of postoperative complications, for example, may further facilitate preoperative decision making[29]. Furthermore, potential advances that could improve patient selection in the future include blood biomarkers (e.g. circulating tumor DNA) and functional magnetic resonance imaging[30–32]. The latter has shown to have a role in the prediction of pathologic complete response to neoadjuvant CRT[31,32].

Important limitations of this study are that it represents a single-institution analysis, where findings may not be generalizable to other centres. Therefore, external validation of the developed nomogram is warranted to determine generalizability[33]. Second, although propensity score matching was performed to improve the comparability between the two treatment groups, unknown confounding factors may have influenced our findings. Third, the absence of a statistical significant benefit of esophagectomy in the high-risk patient may

be due to a lack of power. As such the risk-stratified analysis should be validated in a large population. Despite these limitations, the major strengths of this study include that it is the first demonstration of a clinically applicable nomogram for preoperative prediction of 1-year RFS after esophagectomy, providing detailed analyses of handling variables, model building, validation and calibration according to a standardized template for conducting and reporting of prognostic studies[34]. This will facilitate validation in other populations and incorporation of other factors to improve this model. Also, the ability of the nomogram to make significant distinction between 1-year RFS in another patient group (i.e. the bimodality group) suggests generalizability of the model.

This study demonstrates a novel nomogram that predicts the preoperative probability of early disease recurrence after trimodality therapy for patients with esophageal cancer. The addition of surgery to CRT provided a clear OS benefit in patients low at risk of early disease recurrence. The OS benefit of surgery in high-risk patients was less pronounced. External validation and improvement of the model with new imaging or biomarkers is desired.

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External validation of a nomogram predicting overall survival in patients after neoadjuvant chemoradiotherapy and surgery for esophageal cancer

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ABSTRACT

Objective

Recently a nomogram was developed for the prediction of overall survival (OS) after treatment with neoadjuvant chemoradiotherapy (nCRT) combined with surgery for esophageal or junctional cancer. The nomogram included clinical nodal category (cN), pathological tumour category (ypT) and number of positive lymph nodes in the resection specimen (ypN). The aim of this study was to externally validate the nomogram in an international multi-institutional cohort of patients, and to explore the prognostic use of the nomogram for the prediction of progression-free survival (PFS) after nCRT followed by surgery.

Methods

Patients with potentially resectable esophageal or junctional carcinoma that underwent nCRT plus surgery between 1998 and 2015 at 3 academic centers were included. The discriminative ability of the nomogram for the prediction of OS and PFS was quantified by Harrell's C-statistic. Calibration of the nomogram was visually assessed by plotting actual OS and PFS probabilities against predicted probabilities.

Results

Some 975 patients were included. The discriminative ability of the nomogram for OS was moderate (C-statistic: 0.61) and comparable to that of the initial cohort (C-statistic: 0.63). The nomogram was also useful for the prediction of PFS (C-statistic of 0.64). Calibration of the nomogram was accurate for both OS and PFS, with predicted estimates corresponding closely with the actual observed estimates.

Conclusion

The nomogram accurately predicted OS and PFS after nCRT followed by surgery in an independent international cohort of esophageal cancer patients. The current validated model may enable risk-stratified adjuvant treatment allocation and identify patients in need of routine surveillance after treatment.

INTRODUCTION

Esophageal cancer remains a major public health burden causing over 400.000 deaths annually worldwide[1,2]. For patients with locally advanced non-metastatic esophageal cancer neoadjuvant chemoradiotherapy (nCRT) combined with surgical resection of the esophagus is regarded as standard of care in many countries[3,4]. Despite continuous efforts to improve survival, a substantial number of patients still experience disease progression or tumor-related death after treatment with curative intent[5,6]. Timely and accurate prediction of disease progression and mortality risk may guide follow-up strategies and prompt earlier initiation of interventions to improve survival.

Previous prediction models and staging tools were mainly based on pathologic data from esophageal cancer patients treated with surgery alone. Therefore, Shapiro and colleagues developed a nomogram that predicts overall survival (OS) exclusively in patients treated with nCRT followed by surgery for esophageal or junctional cancer[7]. This prediction model is of special interest as it was constructed in a prospectively collectedmulticenter cohort of patients diagnosed with esophageal cancer, largely derived from the recent CROSS trial[6,7]. Other strengths of are its simplicity and construction in accordance with the most recent recommendations on model development. The proposed model relies on clinicopathologic findings including clinical nodal category (cN), pathological tumor category (ypT) and number of positive lymph nodes in the resection specimen (ypN)[7]. Although the nomogram was internally validated using bootstrapping methods and cross-validation, external validation of the prediction model in an independent set of patients is warranted to ensure external generalizability to different patient populations[8,9].

The aim of this study was to investigate whether the recently introduced nomogram is generalizable to an independent cohort of patients, and to explore the prognostic use of the model for the prediction of progression-free survival (PFS) after nCRT followed by surgery in patients with esophageal or junctional cancer, respectively. An international multi-institutional collaboration was implemented to validate the model externally.

METHODS

This retrospective study has been approved by the institutional review boards of each participating institution and the requirement to obtain informed consent was waived. The study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the checklist from the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement (http://www.tripod-statement.org)[10].

Consecutive patients with locally advanced non-metastatic resectable esophageal or gastro-esophageal junction carcinoma (cT1N+ or cT2-4aN_{any}) who underwent neoadjuvant chemoradiotherapy followed by esophagectomy at 3 major academic institutions were selected from prospectively collected institutional databases (MD Anderson Cancer Center [May 1998 through September 2015; n=638], Mayo clinic [Jan 2007 through June 2012; n=196] and University Medical Center Utrecht [july 2009 trough September 2015; n=141]). Patients were excluded if surgical resection was not completed or if the time interval between completion of chemoradiotherapy and surgery was more than 4 months (indicating salvage surgery). In accordance with the initial published nomogram patients with an incomplete resection (R1) or surgery-related mortality were not excluded of the analysis[7].

Tumors were staged in accordance with the International Union Against Cancer classification that was valid at the time of diagnosis. Staging variables were translated according to the 7th edition for this study – based on the data available in the prospective databases - for uniformity purposes[11]. Initial diagnostic work-up consisted of blood chemistries and hematology, endoscopy with biopsy, endoscopic ultrasound (including fine-needle aspiration if indicated), and either standalone computed tomography with contrast (CT) or integrated ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT scanning for clinical staging. Pre-treatment staging was reasonably comparable to that of the initial nomogram study[7].

Treatment protocol

All patients were discussed in a multidisciplinary conference before initiation of treatment. The (neoadjuvant) treatment regimens in the UMC Utrecht consisted of administration of carboplatin with paclitaxel with 41.4 Gy concurrent radiotherapy[6]. In the MD Anderson Cancer Center and Mayo clinic patients received fluoropyrimidine (5-fluorouracil or capecitabine) with either a platinum and/or a taxane compound[12], with concurrent radiotherapy (41.4, 45 or 50.4 Gy in fractions of 1.8 Gy). After completion of neoadjuvant treatment patients were scheduled for transthoracic (Ivor-Lewis) or transhiatal esophagectomy combined with a two-field lymphadenectomy, with the choice of technique at the discretion of the treating surgeon.

Follow-up

After treatment the most common follow-up schedule included outpatient follow-up visits with an interval of 3 months in the first year, 6 months during the second 2 years, and 12 months until 5 years after treatment or until death. In one center (UMC Utrecht) imaging was only performed in case of a clinical indication and in two centers during every follow-up visit an imaging study (CT or PET-CT), and blood tests were performed (MD Anderson Cancer Center and Mayo Clinic). Overall survival and PFS were calculated from the date of esophagectomy to either the date of death or last follow-up, or the date of disease progression or last follow-up, respectively. Overall survival was censored at 5 years in accordance with the initial prediction model. Death from non-disease-related causes (e.g. myocardial infarction) were censored in the PFS analysis.

Pathological analysis

The resected specimens were processed according to standardized institutional protocols and are presented in accordance with the 7th edition of the International Union Against Cancer ypTNM-classification[11]. The (circumferential) resection margin was evaluated using the College of American Pathologist criteria[13]. The degree of histopathologic tumor regression was graded according to the system proposed by Chirieac and colleagues[14,15].

Statistical analysis

Patient and treatment-related characteristics were described as count with percentages for categorical variables and mean with standard deviation (SD) or median with range for continuous variables. For external validation, the total nomogram points, 1-year OS probability, and 5-year OS probability for each patient in the present cohort were calculated according to the previously published nomogram (Figure 1)[7]. The discriminative ability of the nomogram was evaluated by plotting a Cox regression model, with the total points as only co-variable, and quantified by Harrell's C-statistic[16]. The cohort was categorized into 5 groups based on the nomogram score in ascending order. For each group the observed 1-year and 5-year OS rates were estimated by the Kaplan-Meier method. Calibration, which refers to how closely the predicted probabilities by the nomogram agree with the observed survival probabilities, was visually assessed by plotting actual survival probabilities against predicted survival probabilities for each group. In addition, the predictive ability of the nomogram for OS conditional on the type of treatment (41.4 Gy versus 45 or 50.4 Gy, and Taxane based chemotherapy versus no Taxane, transhiatal versus transthoracic surgery) and hospital was assessed by adding an interaction-term between the nomogram score and type of treatment or hospital.

In order to assess the ability of the nomogram to predict 1-year and 5-year PFS, a Cox regression model was used with the nomogram points as independent variable. The discriminative ability of the nomogram was evaluated using Harrell's C-statistic[16]. For the purpose of PFS prediction, the nomogram score was internally validated using 200 bootstrap resamples, after which the C-statistic was adjusted. The accuracy of the nomogram to predict 1-year and 5-year PFS was visualized with separate calibration plots after bias correction. In order to assess the individual contribution of each explanatory variable - incorporated in the initial nomogram - for the prediction of PFS, cN, ypT and ypN category were entered in a multivariable cox-regression model. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org, 'rms' package). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient and treatment-related characteristics

In the study period some 975 patients were included. The distribution of patient, tumor, and treatment-related characteristic are shown in Table 1. The study population had a mean age of 60.4 years (SD: 9.9 years), and the majority of patients were male (86%). The predominant histologic tumor type was adenocarcinoma (88%), and the most common clinical tumor category was cT3 (82%). The median follow up was 60 months (95% confidence interval [CI]: 54.4-65.6) for the entire cohort. The 5-year OS and 5-year PFS were 48.2% (95% CI: 44.7-51.7) and 51.9% (95% CI: 48.4-55.4), respectively.

External validation of nomogram

A nomogram was previously published to predict 1-year and 5-year survival after neoadjuvant chemoradiotherapy followed by esophagectomy (Figure 1). The variables included in the nomogram were cN, ypT and ypN-category. The discriminative ability of the nomogram for OS was 0.61 in the current cohort of patients compared to 0.63 in the initial cohort. The calibration plots, comparing the predicted OS probabilities with the actual observed survival rates at 1-year and 5-year, are presented in Figure 2. The dotted line represents the optimal line in case of complete concordance between predicted and observed PFS**.** The correspondence between the nomogram estimations of 1-year and 5-year OS and actual observed 1-year and 5-year OS indicated good calibration of the nomogram in the current cohort. The interaction was not statistically significant for any of the different treatment groups (i.e. 41.4 Gy versus 45 or 50.4 Gy [p=0.59], Taxane based chemotherapy versus no Taxane [p=0.358], and transhiatal versus transthoracic surgery [p=0.510]) or hospital (p=0.537), indicating that there was no differential effect of treatment and hospital on the predictive ability of the nomogram.

Prediction of progression-free survival

The discriminative ability of nomogram to predict PFS was reasonable with a C-statistic of 0.64. Internal validation by bootstrapping resulted in an adjusted C-statistic of 0.64, representing hardly any optimism (i.e. 0.003) due to overfitting. Calibration was accurate, with predictions corresponding closely with the actual observed 1-year and 5-year PFS probabilities (Figure 2). The predicted 1-year and 5-year PFS estimations, based on the points provided by the nomogram are presented in Figure 1. The individual clinical variables constituting the 3 components of the nomogram score (i.e. cN, ypT, ypN), were confirmed to be independent prognostic factors of PFS in univariable and multivariable analysis the current cohort of patients (Table 2).

TABLE 1. Patient, tumor, staging, and treatment-related characteristics of patients treated with neoadjuvant chemoradiotherapy followed by surgery for esophageal cancer

Characteristic	**nCRT and surgery (n=975)**		**Missing, n**
	Value	%/SD	n (%)
Gender			0
Female	136	13.9%	
Male	839	86.1%	
Age (years)[a]	60.42	±9.88	0
ECOG performance status			0
0	513	54.5%	
1-2	428	45.4%	
Weight loss			0
<10%	775	79.5%	
>10%	200	20.5%	
Tumor Histology			0
Squamous cell carcinoma	121	12.4%	
Adenocarcinoma	854	87.6%	
Tumor Location			0
Proximal	14	1.4%	
Middle	81	8.3%	
Distal/esophagogastric junction	880	90.3%	
Histologic grade[b]			71 (7.3%)
Good/Moderate	339	34.7%	
Poor	565	57.9%	
EUS-based tumor length (cm)	5.28	±2.72	27 (2.8%)
Clinical T category (seventh)[c]			0
T1	14	1.4%	
T2	141	14.5%	
T3	797	81.7%	
T4	23	2.4%	

TABLE 1 (continued). Patient, tumor, staging, and treatment-related characteristics of patients treated with neoadjuvant chemoradiotherapy followed by surgery for esophageal cancer

Characteristic	**nCRT and surgery (n=975)**		**Missing, n**
	Value	%/SD	n (%)
Clinical N category (seventh)[c]			0
cN0	305	31.3%	
cN1	439	45.0%	
cN2-3	231	23.7%	
Total Radiation dose (Gy)			0
41.4	161	16.5%	
45.0	124	12.7%	
50.4	690	70.8%	
Chemotherapy regimen			
Taxane added	351	64%	
No Taxane added	624	36%	
Surgical approach			0
Transhiatal	49	5.0%	
Transthoracic	926	95.0%	
Number of resected lymphnodes[d]	20	14-26	0
Pathological T-category (seventh)[c]			0
ypT0	304	31.2%	
ypT1	190	19.5%	
ypT2	173	17.7%	
ypT3	302	31.0%	
ypT4	6	0.6%	
Pathological N-category (seventh)[c]			0
ypN0	642	65.8%	
ypN1	210	21.5%	
ypN2	88	9.0%	
ypN3	35	3.6%	
Time to surgery from CRT	54	±18	

Data are numbers, with percentages in parentheses unless indicated otherwise; [a:] Expressed as mean ± SD. [b:] Determined in pretreatment biopsy. [c:] Classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification. [d:] Data are depicted as median *(*interquartile range*)* CRT: chemoradiotherapy.

TABLE 2. Explanatory variables incorporated into the nomogram in association with progression-free survival in patients treated with neoadjuvant chemoradiotherapy followed by surgery for esophageal cancer

Characteristic	1-year PFS estimate[a]	5-year PFS estimate[a]	p-value[a]	Hazard ratio[b] (95% confidence interval)	p-value[b]	Points according to nomogram
cN-category			<0.001			
cN0	86%	58%		reference	-	0
cN+	82%	44%		1.29 (1.03-1.62)	0.030	2
pT-category			<0.001			
ypT0	85%	59%		reference	-	0
ypT1/pT2	83%	49%		1.41 (1.06-1.86)	0.017	2
ypT3	81%	37%		1.90 (1.43-2.54)	0.000	4
pN-category			<0.001			
ypN0	87%	60%		reference	-	0
ypN1	79%	39%		1.55 (1.22-1.97)	<0.001	4
ypN2	77%	21%		2.07 (1.51-2.84)	<0.001	5
ypN3	56%	11%		3.75 (2.45-5.74)	<0.001	10

Grouping of explanatory variables was based on the initial published nomogram[7].PFS: progression-free survival. [a:] based on univariable Kaplan-Meier estimate. [b:]Results of multivariable Cox-Regression analysis of all explanatory variables combined.

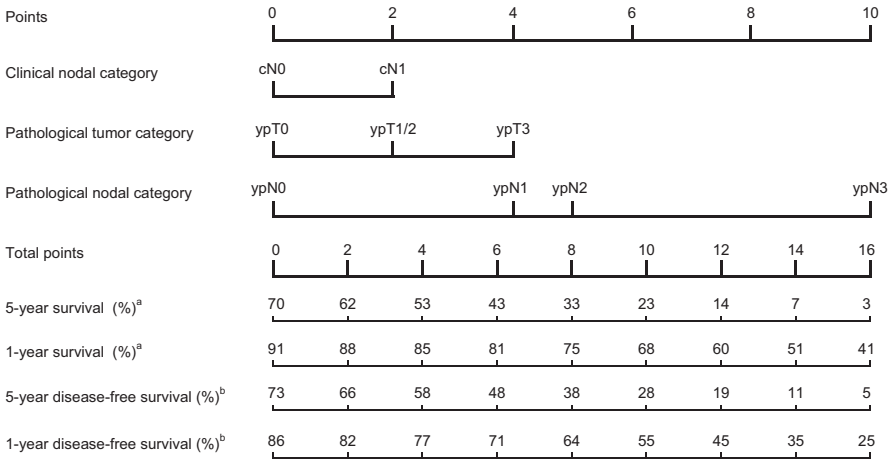

Figure 1. Nomogram for overall survival and disease-free survival in patients with esophageal or esophagogastric junction carcinoma treated with neoadjuvant chemoradiotherapy plus surgery. Figure is adapted from Shapiro et al.[7]. [a:]Estimates derived from initial publication. [b:]Estimates acquired by the current study.

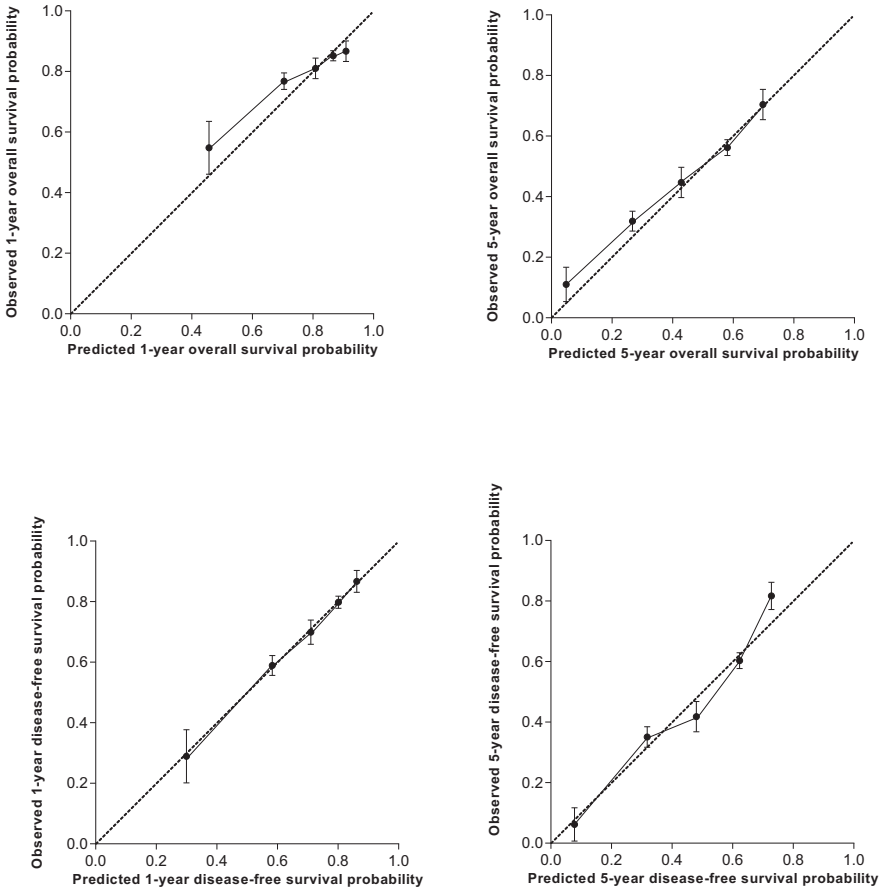

Figure 2. Calibration plot showing the predicted versus the observed probability of 1-year and 5-year overall survival and progression-free survival. The grey line represents the optimal line in case of complete concordance between predicted and observed progression-free survival.

DISCUSSION

This study externally validated a previously published nomogram for the prediction of 1-year and 5-year OS after neoadjuvant chemoradiotherapy with subsequent surgery for esophageal cancer patients in an independent international cohort of 975 patients. The nomogram showed reasonable discrimination – comparable to the initial publication – and calibration showed excellent agreement between predicted and actual observed OS estimates. In addition, prediction of PFS based on the nomogram score showed reasonable discrimination and accurate calibration.

Nomograms have been widely and successfully used for the prediction of survival in different types of cancer[17]. Unfortunately, many nomograms show decreased performance when applied to new patients that were not used to develop the initial prediction model (i.e. external validation)[16]. Reasons for this loss in performance include; optimism of the initial model due to overfitting (random error or noise in the data are fitted rather than generalizable patterns[18]), initial small sample sizes, difference in case mix, or suboptimal development techniques[18,19]. External validation of prognostic models in datasets that were not used to develop the model is therefore essential to assess their actual performance and to enhance their widespread use in clinical practice[9]. To this regard, the results of the current study ensure the reproducibility and reliability of the previously published nomogram to other hospitals and geographical areas, and therewith support its use in clinical practice.

Timely and accurate prediction of OS and PFS after esophageal cancer treatment may guide surveillance strategies and prompt earlier initiation of interventions to improve survival. Given that 36% to 56% [5,12] of the patients undergoing nCRT followed by surgery will experience disease progression after treatment with curative intent, there is currently interest in adjuvant therapies to increase systemic control in patients high at risk of disease progression[20–22]. However, the advantage of adjuvant chemotherapy – in terms of improvement in quality of life and OS – for this group of patients is yet controversial[21,22]. The current NCCN and ESMO guidelines recommend to observe patients with a R0 resection after nCRT regardless of their clinicopahtological characteristics[3,4]. On the other hand, recent cohort studies have shown that adjuvant chemotherapy after nCRT and surgery may improve survival in patients with residual nodal disease[21,22]. This finding, to some extent, indicates that selecting patients based on prognostic factors may allow for better use of resources and be cost efficient. Using a validated nomogram for treatment selection may increase the precision of patient selection because it incorporates multiple clinicopathological features into one PFS estimation. As such

it may also prevent some patients who would not benefit from additional therapy from being exposed to the risk of additional therapy.

The present ESMO and NCCN guidelines do not support routine surveillance for the detection of disease progression after nCRT combined with surgery, as there is currently limited evidence that routine follow-up will impact outcome[3,4]. However, many hospitals will perform routine diagnostic tests for surveillance of asymptomatic patients. The presumed benefit of routine imaging is that early detection of disease progression may improve quality of life and survival[23]. The magnitude of potential benefits, however, must be considered in the light of associated economic costs and likelihood of the potential adverse and unintended effects. The main challenge for the present clinical practice is that currently available routine follow-up protocols perform poorly, as half of the patients (50%) who develop disease progression are detected by the onset of symptoms between apparently normal surveillance scans[23]. Moreover, given that half of the patients will not develop disease progression after treatment[5,12], it could be argued that at least 75% of the patients will not receive benefit from routine follow-up imaging. For this reason one may suggest that surveillance should be tailored to each patients underlying risk of developing disease progression. Increasing the frequency of diagnostic tests in high-risk patients and reducing the frequency in low-risk patients may improve the efficiency of surveilance. The present externally validated nomogram could be a valuable tool in the design of risk-stratified clinical follow-up studies.

The discriminative ability of the present validated nomogram may benefit from further refinement with additional predictors in the future. In line with the original publication, the present study indicates that cN-category holds independent prognostic information beyond ypN-category in patients treated with nCRT followed by esohpagectomy[7]. Due to the effects of chemoradiotherapy, cN-category does not necessarily estimate the same disease category as ypN-category. Although initial clinical staging is notoriously imprecise[24,25], the current study confirms that cN-category holds additional prognostic information beyond pathologic staging. In addition, a recent study found that pre-treatment nodal involvement could be accurately determined in the resection specimen after nCRT, and had better prognostic strength compared to cN-category[26]. This finding indicates that pre-treatment pathological N-category as determined in the resection specimen could be a useful novel prognostic factor that bypasses inaccurate staging and may improve the prediction of PFS and OS in esophageal cancer patients in the future. Furthermore, well recognized prognostic factors, such as involvement of signet ring cells in adenocarcinoma[27,28], extracapsular lymph node involvement[29,30], and tumor biomarkers[31,32] may have additional independent prognostic value beyond the current

nomogram. These factors were not specifically evaluated in the present study, given that the primary aim was to validate the nomogram as initially described.

As the current nomogram relies on the postoperative available pathology results of the resection specimen to predict prognosis after trimodality therapy, it has limited practicality prior to surgery or for patients who do not undergo surgery at al. A previous study has shown that approximately 8% of patients will have interval metastasis after nCRT[33]. These patients in general do not benefit of additional surgery and have a very poor prognosis (median survival of approx. 6 months). In case these patients for some reason (i.e. poor staging) do proceed to surgery, the current nomogram will likely overestimate their prognosis. Furthermore, some patients do not proceed to surgery either because they do not have the physiologic capability to endure surgery or for other reasons (approx. 34%)[34]. In these patients clinicopathological characteristics that are available prior to surgery have to be used to predict their prognosis. A recent study showed that gender, histologic grade, signet ring cell adenocarcinoma, clinical nodal stage, and baseline SUV_{max} can be used as surrogates for prognosis in case no resection specimen is available[34].

Several limitations of the current study must be considered. First, the time span for inclusion of patients was relatively long. Therefore clinical and pathological staging approaches may have changed over time to some extent. Second, interventions for disease progression were performed at physician's discretion, possibly introducing bias to the current study. Moreover, prediction of disease OS and PFS by the current nomogram is not perfect (C-statistic = 0.61 and 0.64, respectively). As previously mentioned, the nomogram may benefit from the incorporation of novel prognostic variables. Rather than developing new models from scratch, researchers should consider improving the current validated model by adding novel predictors[35]. Despite these limitations, strengths of this study include its relatively large number of patients derived from prospective data registries at 3 academic centers to validate an easy to use nomogram for the prediction of survival after nCRT followed by surgery for patients with esophageal cancer.

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Part 2

Treatment response prediction

8

Correlation between functional imaging markers derived from diffusion-weighted MRI and ^{18}F-FDG PET/CT in esophageal cancer

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ABSTRACT

Objective

Both the apparent diffusion coefficient (ADC) acquired by diffusion-weighted magnetic resonance imaging (DW-MRI) and the standardized uptake value (SUV), acquired by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), are well-established functional parameters in cancer imaging. Currently it is unclear whether these two markers provide complementary prognostic and predictive information in esophageal cancer. The aim of this study was to evaluate the correlation between ADC and SUV in patients with esophageal cancer.

Methods

This prospective study included 76 patients with histologically proven esophageal cancer who underwent both DW-MRI and ^{18}F-FDG PET/CT examinations before treatment. The minimum and mean ADC values (ADC_{min} and ADC_{mean}) of the primary tumor were assessed on MRI. Similarly, the glucose metabolism was evaluated by the maximum and mean SUV (SUV_{max} and SUV_{mean}) in the same lesions on ^{18}F-FDG PET/CT images. Spearman's rank correlation coefficients were used to assess the correlation between tumor ADC and SUV values.

Results

The tumor ADC and SUV values as measures of cell density and glucose metabolism, respectively, showed negligible non-significant correlations (ADC_{min} versus SUV_{max}: r=-0.087, p=0.457, ADC_{min} versus SUV_{mean}: r=-0.105, p=0.369, ADC_{mean} versus SUV_{max}: r=-0.099, p=0.349, ADC_{mean} versus SUV_{mean}: r=-0.111, p=0.340). No differences in tumor ADC and SUV values were observed between the different histologic tumor types, stages and differentiation grades.

Conclusion

This study indicates that tumor cellularity derived from DW-MRI and tumor metabolism measured by ^{18}F-FDG PET/CT are independent cellular phenomena in newly diagnosed esophageal cancer. Therefore, tumor ADC and SUV values may have complementary roles as imaging markers in the prediction of survival and evaluation of response to treatment in esophageal cancer.

INTRODUCTION

Esophageal cancer continues to affect more than 450.000 people yearly, and is the sixth leading cause of cancer-related mortality worldwide[1]. Currently, surgical resection of the esophagus combined with neoadjuvant therapy is the cornerstone of curative treatment for patients with non-metastasized esophageal cancer[1–3]. Definitive concurrent chemoradiotherapy is the preferred approach for inoperable locally advanced esophageal cancer[4,5].

Esophageal cancer is usually diagnosed by endoscopy with biopsy and additional multimodality imaging is applied for staging. Since its clinical introduction, whole-body ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET/CT) has emerged as useful adjunct to conventional pre-treatment staging modalities for esophageal cancer[6]. The use of the ^{18}F-FDG tracer allows for quantitative assessment of increased cellular glucose metabolism in tumors by measuring the standardized uptake value (SUV). The SUV is the most commonly used quantitative index of ^{18}F-FDG uptake and is often expressed as its mean (SUV_{mean}) or maximum (SUV_{max}). In a pre-treatment setting the most important value of ^{18}F-FDG PET/CT in the management of esophageal cancer lies in its ability to detect distant metastases and regional lymphadenopathy[7–9]. In addition, ^{18}F-FDG PET/CT has shown potential for the prediction of long-term survival and evaluation of response to treatment[10,11].

Meanwhile, diffusion-weighted magnetic resonance imaging (DW-MRI) is emerging as an advanced imaging technique in esophageal cancer imaging[12–16]. DW-MRI provides functional information based on the variation in (Brownian) motion of water molecules which is a marker for tissue density[17]. The apparent diffusion coefficient (ADC) is a quantitative measure for this variation and inversely correlates with tumor cellularity in various tumors[17], including esophageal cancer[18]. Furthermore, recent exploratory studies have shown that DW-MRI appears to provide valuable information regarding the assessment of response to treatment in esophageal cancer and in several other malignancies[19–22].

Both ADC and SUV values are established parameters in cancer imaging, although they may refer to different aspects of tumor pathophysiology. Currently, it is unclear whether these two imaging markers provide complementary information with regard to the prediction of survival and evaluation of response to treatment in esophageal cancer. Therefore, the purpose of this prospective study was to assess the correlation between SUV and ADC values in order to evaluate whether these values are correlated or independent functional imaging markers in newly diagnosed esophageal cancer.

METHODS

Data were gathered from a multicenter prospective study in which three international cancer centers participated, including The University Medical Center Utrecht (UMCU), The Netherlands Cancer Institute (NKI-AVL), and The University of Texas MD Anderson Cancer Center (MDACC). This prospective study was approved by the institutional review boards of each center separately and written informed consent was provided by all patients. The study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and was registered with ClinicalTrials.gov, number NCT02125448.

Study population

Patients presented at the three participating centers from October 2013 to November 2015 with newly diagnosed biopsy-proven esophageal cancer planned to receive neoadjuvant chemoradiotherapy followed by surgery were eligible for inclusion (Table 1). Exclusion criteria included a history of thoracic radiotherapy, contraindications for MRI, or more than 30 days interval between MRI and ^{18}F-FDG PET/CT imaging. The diagnostic work-up consisted of an endoscopy with biopsy for diagnosis, endoscopic ultrasound, and integrated ^{18}F-FDG PET/CT scan for clinical staging.

MR image acquisition

Patients underwent MRI scanning with anatomical T2-weighted and DW-MRI sequences within two weeks prior to nCRT. The MRI examinations were either performed on a 1.5 Tesla scanner equipped with a 16 or 28-element phased-array receive coil for thoracic imaging (UMCU and NKI-AVL; Achieva or Ingenia; Philips Medical Systems, Best, The Netherlands) or on a 3.0 Tesla scanner equipped with a 32-channel torso phased array coil (MDACC; Discovery, GE Medical Systems, Milwaukee [WI], USA). The MRI scan protocol was specifically developed for esophageal cancer patients and made similar across the three participating centers prior to initiation of the current study[13]. Patients were scanned in supine position without administration of anti-peristaltic agents. Transverse DW-images were obtained under free breathing conditions with the following scan parameters: repetition time 7503 ms, echotime 180ms, slice thickness 4 mm, 50 slices, field of view 260x560mm, voxel size 3.25mm, total acquisition duration was approximately 6 minutes. Three b-values were acquired: 0, 200 and 800 s/mm2. Sagittal and transverse T2-weighted images were obtained with a navigator that monitors the position of the diaphragm using a fast intertwined 1D-MRI acquisition, in order to trigger scanning exclusively during the end of the expiration[23].

^{18}F-FDG PET/CT image acquisition

The ^{18}F-FDG PET/CT examinations were performed on dedicated PET/CT systems (UMCU: mCT, Siemens, Erlangen, Germany; NKI-AVL: Gemini TF, Philips, Cleveland, Ohio; MDACC: Discovery RX, ST, or STE; GE Medical Systems, Milwaukee [WI], USA). Patients underwent injection of ^{18}F-FDG after fasting for at least six hours. Before injection of FDG, blood glucose levels were checked in every patient to excluded hyperglycemia. The activity of intravenously administered ^{18}F-FDG ranged between 190-370 MBq. Imaging started 60-90 minutes after administration of ^{18}F-FDG with a CT for attenuation correction with the following settings: 120 kV, 20-300 mAs, 0.5-s tube rotation time, pitch of 0.813-1.375 and 3-3.75 mm slice width. Following CT, PET scanning was performed from thigh to the base of skull in three-dimensional (3D) acquisition mode with 2 - 5 minutes per bed position. Images were reconstructed using iterative 3D-reconstruction.

Image analysis

All images were quantitatively assessed by authors (LG, SEH, PSNvR) who were trained in DW-MRI and ^{18}F-FDG PET/CT image analysis. These reviewers were blinded to the clinical data, histopathologic results and the ADC maps when measuring ^{18}F-FDG PET/CT images and vice versa. DW-MRI analysis including primary tumor delineation was performed using image analysis software package ITK-SNAP (version 3.4.0)[24]. The primary tumor was delineated on the DW-MR images with a b-value of 800 s/mm^2 using automatic contouring, based on 2 clusters in pre-segmentation mode and default evolution parameters. The DW-MRI images were evaluated quantitatively by calculation of the ADC values for each voxel ($\ln(S_b)=\ln(S_0)-b*ADC$, where S_0 is the signal intensity without diffusion-weighting) with b-values of 0, 200, and 800 s/mm^2[2, 17,20]. Subsequently, the volumes of interest (VOI) on the ADC maps were manually edited by two readers in consensus (LG and SEH) to ensure that only tumor tissue was covered. From the outlined VOI's, the mean and minimum ADC values per VOI were extracted. The mean ADC (ADC_{mean}) was defined as the average ADC value of all voxels in each VOI, and minimum ADC (ADC_{min}) as the lowest 2% percentile.

Based on the reconstructed ^{18}F-FDG PET/CT images the primary tumor volumes were delineated using a semi-automatic gradient-based delineation method followed by manual editing by one reader in commercially available software (MIM Software, Cleveland, OH, USA). This method has been validated in a multi-observer study reporting superior accuracy, consistency and robustness compared with manual and threshold methods[25]. The ^{18}F-FDG uptake in the esophageal tumors as registered on the PET/CT images were evaluated using the SUV. SUV was defined as the ratio of tissue radioactivity concentration (Bq/mL) and

the injected activity (Bq) divided by the body weight (kg*1000). The software automatically calculated the metabolic tumor volume (in cm^3), maximum and mean SUV (SUV_{max} and SUV_{mean}) for each VOI.

Statistical analysis

To assess the strength and direction of correlation between DW-MRI metrics (ADC_{min}, ADC_{mean}) and ^{18}F-FDG PET/CT (SUV_{max}, SUV_{mean}) values Pearson and Spearman correlation coefficients were calculated in case of parametric and non-parametric continuous variables, respectively. Pearson and Spearman's correlation coefficients may be interpreted as follows: a positive or negative correlation coefficient of 0.90–1.00 is considered very high; 0.70–0.89, high; 0.40–0.69, moderate; 0.30–0.49, low; and 0–0.29, negligible[26]. Bland–Altman analysis was used for the assessment of agreement of volume parameters obtained from DW-MRI images and ^{18}F-FDG PET/CT images[27]. Also, the tumor ADC and SUV were compared between squamous cell carcinomas and adenocarcinomas, between moderately and poorly differentiated tumor, and between different clinical T and N-stages using the Student's T-test or Mann–Whitney *U* test, for parametric and non-parametric variables, respectively. Statistical analysis was performed using SPSS 23.0 (IBM Corp. Armonk, NY, USA) and GraphPad Prism 6.07 software (GraphPad Software, La Jolla California USA). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient and tumor characteristics

In the study period, a total of 81 patients with newly diagnosed esophageal cancer who underwent both MRI and ^{18}F-FDG PET/CT were potentially eligible for inclusion. Of these patients, 5 were excluded because the interval between MRI and ^{18}F-FDG PET/CT imaging was more than 30 days (n=4) or the ADC map was of poor quality (n=1). The final study population comprised of 76 patients with a mean age of 61.4 years (standard deviation [SD], 9 years), and 65 (86%) of them were male. Histologic tumor types included adenocarcinoma (n=60, 79%), squamous cell carcinoma (n=13, 17%) or other types (n=3, 4%). The distribution of the esophageal tumor types corresponds with those of western populations. Patient and tumor-related characteristics are presented in Table 1.

Tumor ADC and SUV values

The mean ±SD of the ADC_{mean} and ADC_{min} obtained from the 76 esophageal tumors were $2.05 \pm 0.6 \times 10^{-3} mm^2/s$ and $0.75 \pm 0.04 \times 10^{-3} mm^2/s$, respectively. The average tumor volume as determined by semi-automatic delineation on DW-MRI was 32.6 ±21.4 cm^3 (range, 7.2-85cm^3).

The mean ±SD of the SUV_{mean} and SUV_{max} from ^{18}F-FDG PET/CT were 7.7 ±0.4 and 16.0 ±1.0, respectively. Average metabolic tumor volume measured by semi-automatic ^{18}F-FDG PET/CT contouring was 25.2 ±21.7 cm^3 (range, 2.9-94.0). Figure 1 demonstrates an example of ^{18}F-FDG PET/CT and DW-MRI images in one of the patients.

Correlation analysis of ADC and SUV values

The tumor ADC and SUV values showed negligible non-significant correlations (ADC_{min} versus SUV_{max}: r=-0.087, p=0.457, ADC_{min} versus SUV_{mean}: r=-0.105, p=0.369, ADC_{mean} versus SUV_{max}: r=-0.099, p=0.349, ADC_{mean} vs. SUV_{mean}: r=-0.111, p=0.340). Figure 2 shows the scatter plots of the correlations between the different studied tumor ADC and SUV values.

Comparison between tumor volumes

In Bland-Altman analysis the mean of the difference between DW-MRI-based and ^{18}F-FDG PET-based tumor volumes (and corresponding 95% limits of agreement) was 7.4 cm^3 (-26.9 – 41.7) (Figure 3). On average, the volumes determined on DW-MRI by semi-automatic delineation were larger compared to the volumes determined during semi-automatic contouring on ^{18}F-FDG PET/CT.

Association of tumor ADC and SUV with clinical tumor characteristics

Table 2 shows the difference between functional imaging parameters (tumor ADC and SUV statistics) and established clinical tumor characteristics. In univariable analysis tumor ADC_{mean} and ADC_{min} showed no significant association with histologic tumor type, tumor grade, clinical T-stage and clinical N-stage. Although a trend towards higher SUV values in esophageal squamous cell carcinoma's was observed, SUV_{mean} and SUV_{max} were not significantly associated with tumor characteristics.

TABLE 1. Patient and tumor-related characteristics

Characteristic	**n (%)**
Gender	
Male	65 (86%)
Female	11 (14%)
Age (years)[a]	61.4 ± 9.4
Histologic tumor type	
Adenocarcinoma	60 (79%)
Squamous cell carcinoma	13 (17%)
Other	3 (4%)
Histologic tumor grade	
Moderate differentiation	43 (57%)
Poor differentiation	33 (43%)
Tumor location	
Proximal third	2 (3%)
Middle third	9 (12%)
Distal third	49 (65%)
Gastro-esophageal junction	16 (20%)
Clinical T-stage	
cT2	12 (15%)
cT3	62 (82%)
cT4	2 (3%)
Clinical N-stage	
cN0	25 (33%)
cN1	30 (40%)
cN2	20 (26%)
cN3	1 (1%)
Interval PET/MRI in days[b]	17 (0-30)
ADC_{mean} (10^{-3} mm^2/s)[a]	2.05 ± 0.6
ADC_{min} (10^{-3} mm^2/s)[a]	0.75 ± 0.4
SUV_{mean} [a]	0.77 ± 0.4
SUV_{max} [a]	1.60 ± 1.0

[a] Data presented as mean ± standard deviation. [b] Data presented as median with range

TABLE 2. Association of tumor ADC and SUV with clinical tumor characteristics

Variable	n	Mean ADC ($*10^{-3}mm^2/s$)	*p*	Lowest ADC ($*10^{-3}mm^2/s$)	*p*	Mean SUV	*p*	Maximum SUV	*p*
Histologic tumor type*									
Adenocarcinoma	60	2.10 ± 0.6	0.289	0.75 ± 0.4	0.556	7.5 ± 3.5	0.068	15.7 ± 9.1	0.180
Squamous cell ca.	13	1.90 ± 0.3		0.82 ± 0.3		9.2 ± 3.6		18.3 ± 8.6	
Histologic tumor grade									
Moderate	43	1.97 ± 0.6	0.215	0.72 ± 0.4	0.535	7.4 ± 3.5	0.376	14.9 ± 8.0	0.247
Poor	33	2.15 ± 0.6		0.78 ± 0.4		8.1 ± 3.6		17.5 ± 9.9	
Clinical T-stage									
cT2	12	1.96 ± 0.6	0.567	0.60 ± 0.4	0.173	8.0 ± 3.3	0.574	16.7 ± 8.7	0.729
≥cT3	64	2.06 ± 0.6		0.77 ± 0.4		7.7 ± 3.6		15.9 ± 9.0	
Clinical N-stage									
cN0	25	1.90 ± 0.6	0.140	0.70 ± 0.4	0.471	7.5 ± 3.7	0.514	14.7 ± 8.9	0.216
cN+	51	2.12 ± 0.6		0.77 ± 0.4		7.9 ± 3.4		16.7 ± 8.9	

Data presented as mean ± standard deviation. ADC: Apparent diffusion coefficient. SUV: Standardized uptake value.*Patients with other histologic tumor types than adenocarcinoma and squamous cell carcinoma were excluded from this analysis.

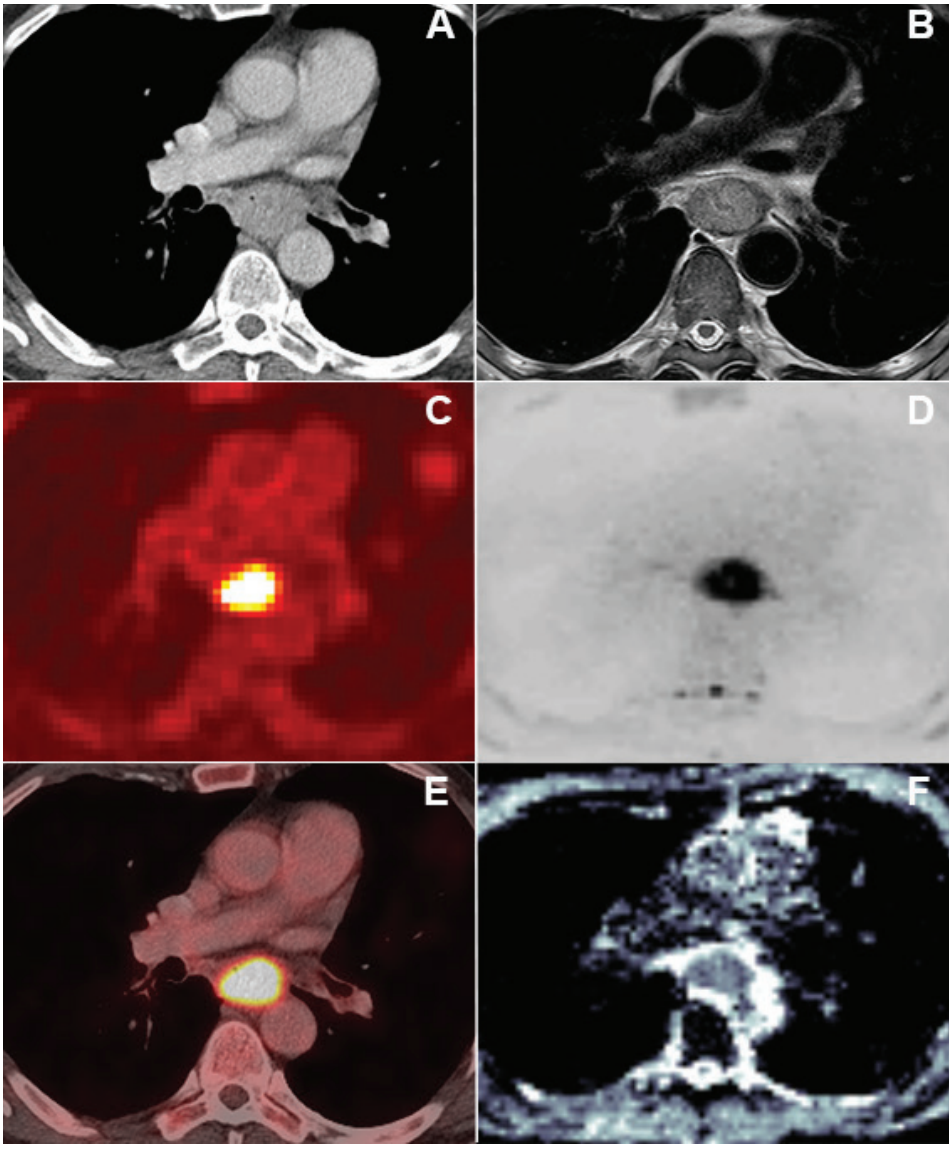

Figure 1. Example of a mid-esophageal adenocarcinoma of a 72 year old male patient. CT (**A**) demonstrates a round-shaped esophageal tumor with high uptake on ^{18}F-FDG PET (**C**) and the fused images (**E**). Corresponding tumor on T2-weighted imaging (**B**) with high signal on DWI-MRI (b=800 s/mm^2) (**D**) and corresponding ADC map (**F**) with restricted diffusion at the location of the tumor.

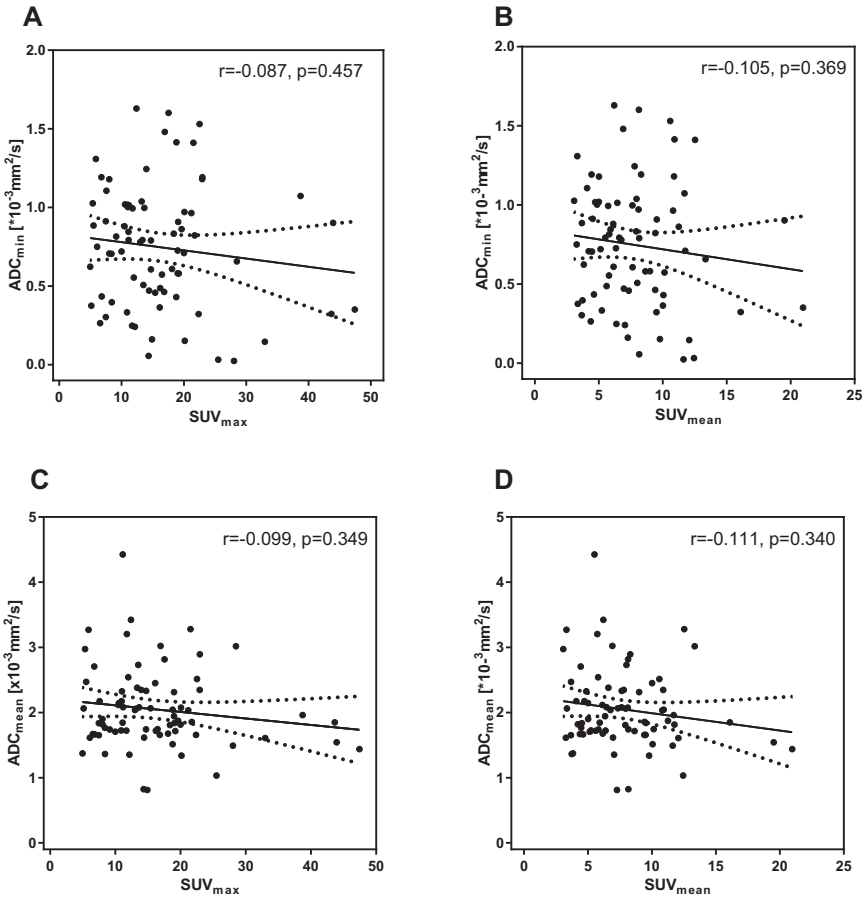

Figure 2. Scatter plots of correlation between tumor ADC and SUV values as determined on DW-MRI and ^{18}F-FDG PET/CT imaging from 76 esophageal cancer tumors. For each scatterplot, the best-fit line is shown as the solid line. Dotted lines above and below represent the upper and lower 95% confidence intervals. **A**: ADC_{min} vs. SUV_{max}. **B**: ADC_{min} vs. SUV_{mean}. **C**: ADC_{mean} vs. SUV_{max}. **D**: ADC_{mean} vs. SUV_{mean}.

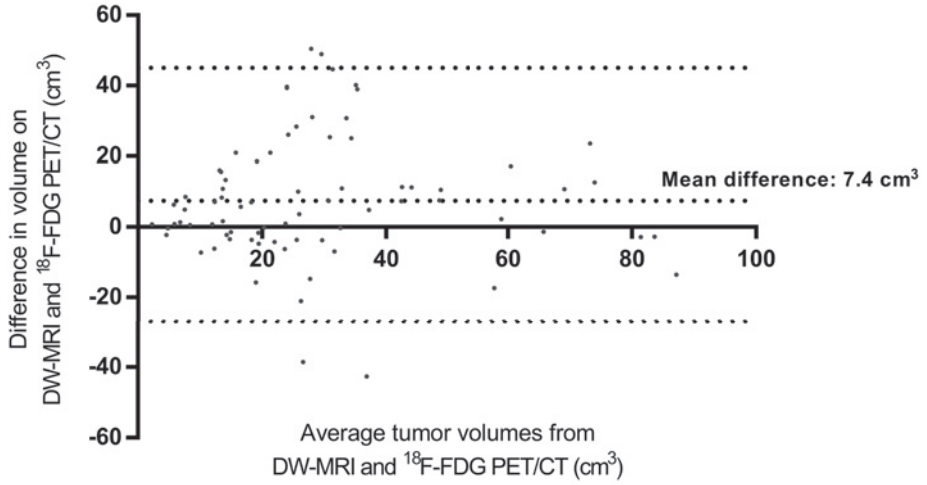

Figure 3. Bland-Altman plot comparing tumor volumes delineated on DW-MRI versus ^{18}F-FDG PET/CT, respectively. The y-axis shows the difference between the two volumes (in cm^3), and the x-axis shows the mean of the two volumes. The black dotted lines represent the upper and lower 95% limits of agreement.

DISCUSSION

In this multi-center prospective study, correlations between functional imaging markers derived from DW-MRI and ^{18}F-FDG PET/CT imaging were evaluated. The results of the current study show that it was feasible to obtain complete data sets of both imaging modalities from most patients with newly diagnosed resectable esophageal cancer. No correlations were found between tumor ADC and SUV, regardless of the underlying histological subtype. Also, no associations of ADC and/or SUV with tumor stage or grade were found.

In order to assess potential clinical complementarity of tumor ADC and SUV values for prediction of survival or evaluation of response to treatment in esophageal cancer, the current study investigated the correlation between these two parameters. Assessment of treatment response is an important new determinant of prognosis, and guide towards more individualized treatment decisions for patients with locally advanced esophageal cancer[28,29]. Due to the unsatisfactory results in treatment response assessment of currently available diagnostic techniques (i.e. endoscopic ultrasonography[30], endoscopy with biopsy[30], and ^{18}F-FDG PET/CT[10,11,31]), the utility of DW-MRI for response assessment in esophageal cancer is currently of high clinical interest. Although sequential ^{18}F-FDG PET/CT scanning has shown to be moderately predictive for treatment response[10,11], ADC changes have shown great potential as marker for the degree of response to treatment in esophageal cancer[20]. The combination

of these two functional imaging techniques may provide additional information with regard to tumor characterization.

Similar to our findings, previous studies assessing other types of cancer found no correlation between pretreatment tumor ADC and SUV values[32–36]. These results suggest that increased metabolic activity and restricted water diffusion represent independent phenomena and refer to different aspects of tumor pathophysiology. Combining multiparametric functional MRI with metabolic information derived from ^{18}F-FDG PET/CT may therefore provide complementary information[33,36].

Meanwhile, other studies comparing ADC and SUV in other types of cancer did observe a significant correlation between tumor ADC and SUV values[37–43]. However, the reported correlation coefficients in some of these studies actually indicated a weak correlation (0-0.40)[39,42,43].

Several factors may account for the difference in literature with regard to reported correlations between tumor ADC and SUV. First, performing functional imaging in different types of cancer (e.g. ovarian and colorectal cancer lesions) results in significant different ADC and SUV values[36]. The heterogeneous outcomes of functional metrics in different types of cancer may partially account for this difference[40]. Second, several studies calculated the ADC_{mean} by taking averages of the mean ADC values of each separate image slice, regardless of the cross sectional size of the tumor on each slice[37–39]. In the current study the weighted average of all voxels of the entire VOI was taking into account, which results in a closer resemblance of the mean ADC of the whole tumor.

Tumor volume delineation was assessed on DW-MRI, and if necessary adapted after critical evaluation on the ADC maps. Although in general T2-weighted images provide more anatomical details, this method ensured that the calculation of ADC was solely based on parameters obtained from high signal on DWI-MRI. A reasonable agreement of tumor volumes delineated on DW-MRI and ^{18}F-FDG PET/CT was demonstrated in the Bland-Altman plot. On average, tumor volumes measured on DW-MRI were 7 cm^3 larger than those measured on ^{18}F-FDG PET/CT. These findings correspond with the results of previous studies that found smaller tumor volumes on PET compared to DW-MRI imaging[37,44,45]. For the delineations on PET, a validated method with higher consistency compared to manual and thresholding methods was used[25] However, MRI-based delineation in esophageal cancer tumors is relatively new. Currently, there is no consensus for accurate determination of tumor boundaries on MRI.

Therefore, additional investigations aim to develop consensus on optimal MR delineation definitions for esophageal cancer.

Previous studies have reported associations between pre-treatment tumor ADC or SUV values, and histologic tumor characteristics (i.e. adenocarcinoma versus squamous cell carcinoma, tumor differentiation and cTN stage) in esophageal cancer[16,20,46,47]. The current study found a trend towards higher SUV values in esophageal squamous cell carcinoma's, which is supported by previous studies[46,47]. However, other associations could not be reproduced, which may be due to substantial differences in study population characteristics and sample size among the studies. Concerning ADC values, previous reports so far reported equivocal results, but were exploratory by nature and included a limited number of patients[20,45].

Several limitations apply to this study. Factors potentially influencing the generalizability of the results include the hardware characteristics (i.e. different MRI and PET/CT systems), chosen imaging parameters and applied delineation techniques. Interobserver agreement analysis of ADC tumor delineation with a semi-automatic approach were not part of this study and need further elucidation. Moreover, the comparison between the imaging parameters (tumor ADC and SUV) and tumor characteristics (i.e. T-stage and histology) was based on small numbers which may have resulted in type 2 errors. Finally, pretreatment ADC, SUV and volume measurements could not be correlated to surgical pathology parameters, as the surgical specimens were obtained after neoadjuvant treatment in the current study. With respect to the aforementioned limitations, future comparative studies are needed to elucidate the advantages and disadvantages of DW-MRI and ^{18}F-FDG PET/CT imaging in esophageal cancer. These studies may include comparison of DWI and PET parameters at multiple time points during treatment.

This study indicates that both tumor cellularity measured by DW-MRI imaging and tumor metabolism by ^{18}F-FDG PET/CT are independent cellular phenomena in newly diagnosed esophageal cancer. Therefore, ADC and SUV values may have complementary roles as imaging markers in the prediction of survival and evaluation of response to treatment in esophageal cancer.

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9

DW-MRI and DCE-MRI are of complementary value in predicting pathologic response to neoadjuvant chemoradiotherapy for esophageal cancer

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ABSTRACT

Objective

To explore the potential benefit and complementary value of a multiparametric approach using diffusion-weighted (DW-) and dynamic contrast-enhanced (DCE-) magnetic resonance imaging (MRI) for prediction of response to neoadjuvant chemoradiotherapy (nCRT) in esophageal cancer.

Methods

Forty-five patients underwent both DW-MRI and DCE-MRI prior to nCRT (pre), during nCRT (week 2-3) (per) and after completion of nCRT, but prior to esophagectomy (post). Subsequently, histopathologic tumor regression grade (TRG) was assessed. Tumor apparent diffusion coefficient (ADC) and area-under-the-concentration time curve (AUC) were calculated for DW-MRI and DCE-MRI, respectively. The ability of these parameters to predict pathologic complete response (pCR, TRG1) or good response (GR, TRG≤2) to nCRT was assessed. Furthermore the complementary value of DW-MRI and DCE-MRI was investigated.

Results

GR was found in 22 (49%) patients, of which 10 (22%) patients showed pCR. For DW-MRI, the 75th percentile (P75) $\Delta ADC_{post\text{-}pre}$ was most predictive for GR (c-index=0.75). For DCE-MRI, P90 $\Delta AUC_{per\text{-}pre}$ was most predictive for pCR (c-index=0.79). Multivariable logistic regression analyses showed complementary value when combining DW-MRI and DCE-MRI for pCR prediction (c-index=0.89).

Conclusion

Both DW-MRI and DCE-MRI are promising in predicting response to nCRT in esophageal cancer. Combining both modalities provides complementary information, resulting in a higher predictive value.

INTRODUCTION

Worldwide esophageal carcinoma continues to affect more than 450.000 people annually, with 5-year overall survival rates rarely exceeding 35%[1–3]. Currently, neoadjuvant chemoradiotherapy (nCRT) followed by surgery is considered standard of care for patients with resectable locally advanced esophageal cancer. Many studies have reported that the degree of response to neoadjuvant therapy is associated with patient prognosis, with pathologic complete response (pCR) having the most favorable long-term prognosis[1,4–7]. Accurate prediction of good response to nCRT potentially allows a wait-and-see approach, with omission of surgery and close clinical follow-up. On the other hand, accurate prediction of poor response allows early treatment modification, e.g. intensification of neoadjuvant therapy or primary surgery.

Unfortunately, diagnostic modalities – including endoscopic biopsy, endoscopic ultrasonography and computed tomography (CT) – that are currently used to identify pathologic response yield unsatisfactory results[8,9]. Highest overall pooled sensitivities and specificities were found for ^{18}F-FDG-PET(/CT), however, with values ranging from 67% to 70% this is still insufficient to justify changes in clinical decision-making[10,11]. Meanwhile, functional MRI techniques are emerging as an advanced imaging technique since it visualizes different and possibly complementary tumor characteristics. With diffusion-weighted (DW-) magnetic resonance imaging (MRI) the variation in free diffusion of water molecules between different tissues is visualized, allowing it to distinguish tumorous (dense) tissue from healthy tissue using the apparent diffusion coefficient (ADC)[12–15]. With dynamic contrast-enhanced (DCE-) MRI, the vascular integrity is visualized using administration of a contrast agent, allowing it to distinguish neoplastic changes in tissue[16]. Two recent pilot studies reported that tumor alteration on both DW-MRI and DCE-MR imaging during the first 2-3 weeks of nCRT for esophageal cancer are highly predictive for pCR[17,18]. However, these findings have not yet been validated in a larger cohort. Also, no direct comparison between DW-MRI and DCE-MRI for treatment response evaluation in this setting has been reported.

The purpose of the current study was to evaluate, in a multicenter setting, whether combining data from both DW-MRI and DCE-MRI in patients receiving nCRT for esophageal cancer yields complementary information for response prediction, and may therefore increase predictive power compared to single technique MR imaging.

METHODS

Study population

Patients were included in the University Medical Center Utrecht (UMCU) and in the Netherlands Cancer Institute (NKI), from August 2013 to January 2016. Written informed consent was obtained from all patients and this study was approved by the institutional review board of each center. Patients with contraindications for 1.5T MRI with administration of a contrast agent were not eligible for inclusion. All 46 patients with biopsy-proven esophageal cancer receiving nCRT followed by surgery who underwent all MRI studies were initially included in this study. One patient was excluded due to a very small tumor volume (<2.5mL on the initial scan). Of the remaining patients, 31 were scanned in the UMCU and 14 in the NKI (Table 1).

Treatment protocol

All patients included in this study were planned to receive weekly administration of intravenous carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m^2 body surface-area) for 5 weeks, with concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy [1]. All patients were treated with intensity modulated radiation therapy (IMRT) or volumetric modulated arc radiotherapy (VMAT), planning goals were to cover at least 99% of the target volume with 95% of the prescribed dose. Five to ten weeks (median 8 weeks) after completion of neoadjuvant treatment, all patients underwent a transhiatal or transthoracic esophagectomy.

Histopathologic assessment

Histopathologic assessment of the resection specimen was performed by a dedicated pathologist with GI subspecialty according to Mandard, with a tumor regression grade (TRG) ranging from 1 (pCR) to 5 (absence of regressive changes)[19]. Two approaches were applied to discriminate between response to treatment: an analysis was performed to differentiate between patients with good (GR, TRG≤2) versus poor response (noGR, TRG≥3), and pathologic complete response (pCR, TRG1) versus no pathologic complete response (no-pCR, TRG≥2).

MRI acquisition

Acquisition of MR images was performed at three time points: a baseline scan prior to treatment (pre), a scan after two weeks (8-13 fractions) of nCRT treatment (per) and a preoperative scan 3-9 weeks after completion of nCRT treatment (post). In all patients there was a similar initial intention to schedule surgery 6-8 weeks after completion of nCRT and plan the post-scan within two weeks prior to surgery. All image acquisition was performed

on a 1.5T Philips Achieva or Ingenia (Best, The Netherlands) using the Torso (16 channels) or Anterior/Posterior (28 channels) receive coils, respectively. The same imaging protocol was used in both institutes. DWI scans were acquired in transverse plane during free breathing, for three different b-values (0, 200, 800 s/mm^2), with a bandwidth per pixel of 29.4 or 23.4 Hz for the Achieva and Ingenia, respectively. The DCE-series consisted of 62 3D scans, scanned with a temporal resolution of 3 seconds. After the 10th scan the contrast agent was injected with an automatic syringe pump at a flow rate of 1 mL/sec (for patients >100kg 2mL/sec), followed by a saline injection. In the UMCU gadobutrol (Gd-BT-DO3A, Gadovist; Schering AG, Berlin, Germany) was used at a dose of 0.1 mmol/kg of body weight, at the NKI Dotarem (Gadoteric acid, 0.5 mM; Guerbet, Paris, France) was used with a fixed dose of 7.5 mmol for each patient. In order to prevent artifacts in the aorta due to pulsatile flow, the heart was included in the scanned volume. Prior to the DCE scan, a transverse T_2-weighted scan was acquired for anatomical verification with a multi-slice turbo spin echo sequence, using a navigator for respiratory triggering[17,18]. Detailed scanning parameters are presented in Table 2.

Image analysis

DWI scans were corrected for geometric distortions using a B_0-field inhomogeneity map[20] and ADC values were calculated using a mono-exponential model. DCE scans were processed according to a previously reported protocol[18]. Rigid registration was performed to account for motion between scans. A series of scans with variable flip-angles were acquired. This enabled quantification of the intrinsic tissue T_1 time which is required to quantify the contrast agent concentration after injection[21]. The area-under-the-concentration versus time curve (AUC), defined as an integral over 60 seconds after inflow of contrast, was calculated. Examples of a T_2-weighted, a DWI and a DCE scan and the corresponding ADC- and AUC-maps are shown in Figure 1. To minimize inter-observer variability, the primary tumor was automatically delineated on the initial b800 DWI using a contouring algorithm in ITK-SNAP v3.4.0.QT4 with 2 clusters in pre-segmentation mode and default evolution parameters[22]. As a result, a region with high values on the b800 DWI was delineated. These automatic delineations were verified and manually adjusted if necessary (e.g. in case of volume overestimation or the inclusion of lymph nodes), using both the ADC-map and T_2-weighted scan in Volumetool, an in-house developed image software tool[23]. This pre-delineation was registered to the next time point (per) and manually adjusted for possible shrinkage in the circumference of the esophagus, which was then propagated to the final time point (post), again followed by manual adjustments if necessary. In other words, in each individual patient the cranio-caudal length of the delineations remained constant over the three time points. All adjustments were performed in consensus by two readers (S.E.H. and L.G.) and verified by a radiation oncologist (S.M.).

Data analysis

In line with our previous work[17,18], mean, median and several percentiles (P75/P90) were calculated for ADC (DW-MRI) and AUC (DCE-MRI) within the delineations on both modalities. Separate time points as well as percentage differences between time points were analyzed. The first acquired scan was used as a reference for these calculations, as this was found to provide the highest predictive performance in the prior studies on DW-MRI or DCE-MRI. Previously published optimal thresholds for both modalities were reoptimized in this larger patient cohort.

A quantitative quality assessment was performed on all DW-MRI scans because some scans were visually of poor quality. Scans with poor quality typically showed high noise levels in the lung and/or poor visibility of the spleen, therefore on the b800 DWI both organs were delineated and mean signal values were divided to reach a quantitative quality measure (spleen/lung). The analysis of the DW-MRI and a combined analysis of DW-MRI and DCE-MRI was only performed in scans in which the aforementioned quality measure was higher than mean minus standard deviation (SD) of the whole patient group.

Statistical analysis

Patient and treatment-related characteristics were described as count with percentages or mean with SD as appropriate. The association between response and DW-MRI or DCE-MRI parameters was estimated using univariable logistic regression analysis. Diagnostic performance measures (i.e. sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)) were computed and receiver operating characteristics (ROC) curve analysis was performed, calculating the area-under-the-curve (c-index). Complementary value of DW-MRI and DCE-MRI was assessed using a multivariable logistic regression model. Model performance was assessed by the Akaike Information criterion[24]. Predictive values were only presented when DW-MRI and DCE-MRI were complementary. Ideal cut-off values were calculated by giving equal weight to sensitivity and specificity. The probability of pCR (output of logistic regression) based on a the imaging modalities can then be calculated with following the equation:

$$\text{Probability (pr)} = \frac{\exp(\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_n X_n)}{1+\exp(\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_n X_n)} \quad (1)$$

with n the number of variables X (univariable [n=1], techniques combined [n=2]), and α/β constants calculated by the logistic regression model. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed in SPSS Statistics version

22 (IBM Corp., Armonk, NY, USA) and visual representations using GraphPad Prism 6.07 software (GraphPad Software, La Jolla, CA, USA).

TABLE 1: Patient and treatment-related characteristics for both institutes. The patient characteristics from the combined analysis are summarized in the third column

	Study population UMCU (n=31)	**Study population NKI** (n=14)	**Combined analysis DCE/DWI UMCU + NKI** (n=34)
Gender			
Male	27	11	29
Female	4	3	5
Age, years (at start nCRT)*	64.5 ± 7.6	58.6 ± 13.0	62.4 ± 10.1
Clinical T-stage			
T2	6 (19%)	2 (14%)	5 (15%)
T3	25 (81%)	12 (86%)	29 (85%)
Clinical N-stage			
N0	9 (29%)	6 (43%)	10 (29%)
N1	8 (26%)	5 (36%)	12 (35%)
N2	12 (39%)	3 (21%)	9 (26%)
N3	2 (6%)	0 (0%)	3 (9%)
Type			
SCC	3 (10%)	2 (14%)	4 (12%)
AC	26 (84%)	12 (86%)	28 (82%)
ASC	2 (6%)	0 (0%)	2 (6%)
Location			
Proximal third of esophagus	1 (3%)	0 (0%)	1 (3%)
Middle third of esophagus	3 (10%)	1 (7%)	3 (9%)
Distal third of esophagus	23 (74%)	6 (43%)	21 (62%)
Gastroesophageal junction	4 (13%)	7 (50%)	9 (26%)
Acquisition, nr of days			
Pre (before start nCRT)*	6 (2-14)	5 (-1-11)	6 (-1-14)
Per (after start nCRT)*	10 (8-17)	15 (9-16)	10 (8-17)
Post (after completion nCRT)*	41 (17-62)	39 (31-65)	40.5 (17-57)
Post scan - surgery interval*	10 (5-48)	11.5 (4-19)	11.5 (4-48)

SCC = squamous cell carcinoma; AC = adenocarcinoma ; ASC = adenosquamous carcinoma
NOTE – Data presented as counts with percentages in the parentheses unless stated otherwise
* Data presented as median (range)

TABLE 2. Scan parameters of the used MRI protocol

	DWI EPI (STIR)	**DCE (3D – FFE T_1W)**	**T_2W (MS-TSE)**	**B_0 (Dual acquisition)**
Scan plane	transverse	coronal	transverse	Transverse
Slice thickness (mm)	4.00	3.00	4.00 (gap: 2.48)	4.00
Voxel size (mm)	3.25	1.18 or 1.98*	0.67	4.06
TR (ms)	7241	3.43	1604	630.4
TE (ms) (TE_2)	76.2	1.53	100	4.6 (9.2)
Flip angle (˚)	90	20	90	30
Temporal resolution (sec)	N.A.	3	N.A.	N.A.
Number of time frames	N.A.	62	N.A.	N.A.
b-values (s/mm^2)	0,200,800	N.A.	N.A.	N.A.

N.A. = not applicable ; * second parameter applicable for scans acquired with Ingenia scanner

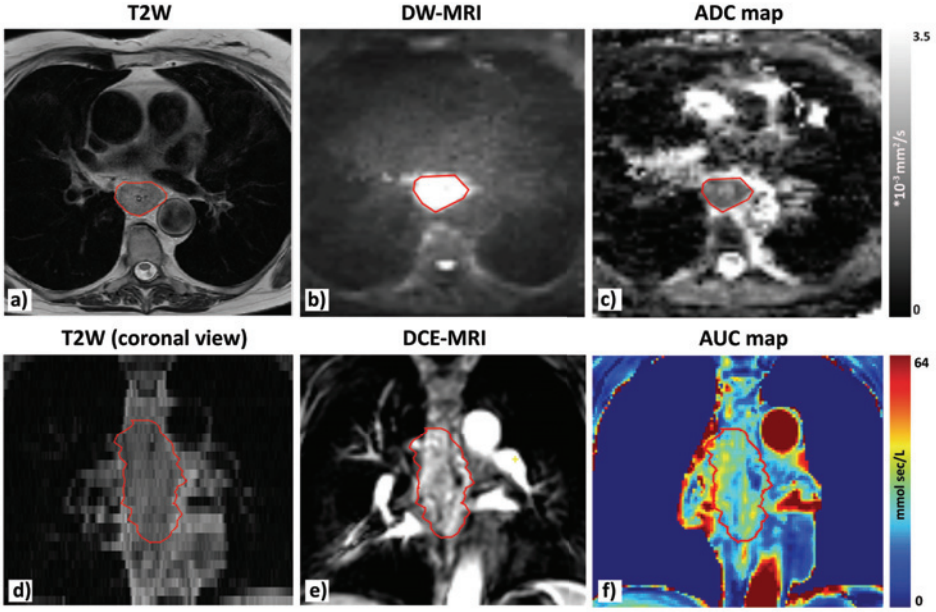

Figure 1. An example of acquired MRI scans for one patient for one time point (pre scan). In (a) a T_2W scan is shown with in (d) the coronal view of the same scan. (b) A b800 DW-MRI scan and its corresponding ADC-map in (c). In (e) the 24th scan of a DCE-MRI series is shown, during inflow of contrast in the tumor. Corresponding calculated AUC-map is found in (f).

RESULTS

For the total group of 45 patients, assessment of the histopathologic tumor type revealed adenocarcinoma in 38 (84%) patients, squamous cell carcinoma in 5 (11%) patients, and adenosquamous carcinoma in 2 (4%) patients. Patient- and treatment-related characteristics

are shown in Table 1. The resection specimen showed good response (TRG 1-2) in 22 (49%) patients, of which 10 (22%) patients showed pCR .

DCE-MRI parameter AUC_{per} 90th percentile (P90) showed a significant difference in separating pCR from no-pCR (p=0.044, c-index=0.72). An initial increase followed by a decrease was found when comparing the three time points. AUC P90 showed for pCR values of 34.0 ± 9.4 mmol·L^{-1}s [mean ± SD], 36.8 ± 8.3 mmol·L^{-1}s and 29.5 ± 13.9 mmol·L^{-1}s for pre, per and post, respectively. Similarly, AUC P90 for no-pCR was 34.3 ± 9.5 mmol·L^{-1}s, 48.9 ± 16.1 mmol·L^{-1}s and 32.0 ± 9.6 mmol·L^{-1}s, for pre, per and post, respectively. When comparing differences between scans with respect to the first time point, the most predictive value to separate pCR from no-pCR, was the relative increase in tumor AUC with a P90 $\Delta AUC_{per\text{-}pre}$ of 10.6% ± 17.6% and 45.2% ± 41.5% for pCR and no-pCR, respectively (p=0.028, c-index=0.79) (Figure 2a,b). No significant differences were found for ΔAUC in predicting GR versus noGR (Table 3).

Quantitative quality assessment of the b800 maps for the three different time points resulted in spleen/lung image intensity ratio [mean ± SD] values of 5.9 ± 2.0, 5.0 ± 1.7 and 4.4 ± 1.7 for pre, per and post scans, respectively. A total of 24 out of 138 (17%) scans revealed a value below mean-SD, with a large overlap within the same patients for the three time points. This resulted in exclusion of 11 patients (AVL [n=5] and UMCU [n=6]), of which 7 GR and 4 noGR (Table 1, 3rd column). No direct relation was found between excluded patients and patient and treatment-related characteristics (e.g. TN-stage, tumor location). For the remaining 34 patients, analysis was performed on DW-MRI parameter ADC. Analysis of the three time points showed only a significant difference in separating GR from noGR for ADC_{per} P90 (p=0.040, c-index=0.70) and ADC_{post} P90 (p=0.040, c-index=0.70). An increasing trend in ADC over time was found for both good and poor responders (median ADC for GR 1.87 ± 0.41*10^{-3} mm^2/s [mean ± SD], 2.31 ± 0.37*10^{-3} mm^2/s and 2.72 ± 0.62*10^{-3} mm^2/s for pre, per and post, respectively, and for noGR 1.96 ± 0.32*10^{-3} mm^2/s, 2.15 ± 0.37*10^{-3} mm^2/s and 2.41 ± 0.51*10^{-3} mm^2/s). Significant associations with response were found in ΔADC with respect to the first time point. $\Delta ADC_{per\text{-}pre}$ P90 resulted in a [mean ± SD] of 23.5% ± 20.5% and 9.8% ± 11.7% for GR and noGR respectively (p=0.035, c-index=0.70). The most predictive parameter was $\Delta ADC_{post\text{-}pre}$ P75 with [mean ± SD] of 45.0% ± 25.3% and 23.1% ± 25.2% for GR and noGR respectively (p=0.031, c-index=0.75) (Figure 2c,d). Analysis of ΔADC in predicting pCR versus no-pCR did not show significant associations (Table 3).

Multivariable logistic regression analysis, including patients for whom both DW-MRI and DCE-MRI were available (n=34), revealed that these parameters were complementary in

predicting pCR (c-index=0.89). Predictive values of this model and the univariable analysis are presented in Table 3. The $\Delta AUC_{per\text{-}pre}$ as function of $\Delta ADC_{post\text{-}pre}$ is presented in Figure 3 in which threshold lines of both univariable models as well as the multivariable model are shown. The ROC-curves of the logistic regression models are shown in Online Supplementary Figure 1a for both GR and pCR, in which the chosen threshold for the complementary model predicting pCR is marked. Since percentile values are not commonly produced in analysis software, predictive values and ROC-curves are also presented for mean $\Delta AUC_{per\text{-}pre}$ and $\Delta ADC_{post\text{-}pre}$ in Online Supplementary Table 1 and Online Supplementary Figure 1b. Slightly lower c-index and predictive values were reached, multivariable logistic regression showed no complementary value.

TABLE 3. Predictive values for both DW-MRI and DCE-MRI discriminating pCR versus no-pCR and GR versus noGR. Only the most predictive parameters are shown. Also a combined analysis of both DW-MRI and DCE-MRI in multivariable logistic regression is presented

	n	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	c-index	p-value
GR vs. noGR								
P90 $\Delta AUC_{per\text{-}pre}$	45	33.7%	68.2	56.5	60	65	0.64	0.261
P75 $\Delta ADC_{post\text{-}pre}$	34	22.4%	86.7	57.9	61.9	84.6	0.75	0.031
pCR vs. no-pCR								
P90 $\Delta AUC_{per\text{-}pre}$	45	27.7%	90	62.9	40.9	95.7	0.79	0.028
P75 $\Delta ADC_{post\text{-}pre}$	34	29.5%	83.3	53.6	27.8	93.8	0.76	0.050
Combined	34	0.138*	100	75	46	100	0.89	0.086/0.052**

GR = good response, pCR = pathologic complete response, P90/P75 = 90th and 75th percentiles, respectively
* probability value following Equation 1 with model values: α=-2.244, β_{AUC}=-0.034 and β_{ADC}=0.044
** for P90 $\Delta AUC_{per\text{-}pre}$ and P75 $\Delta ADC_{post\text{-}pre}$ respectively in multivariable analysis

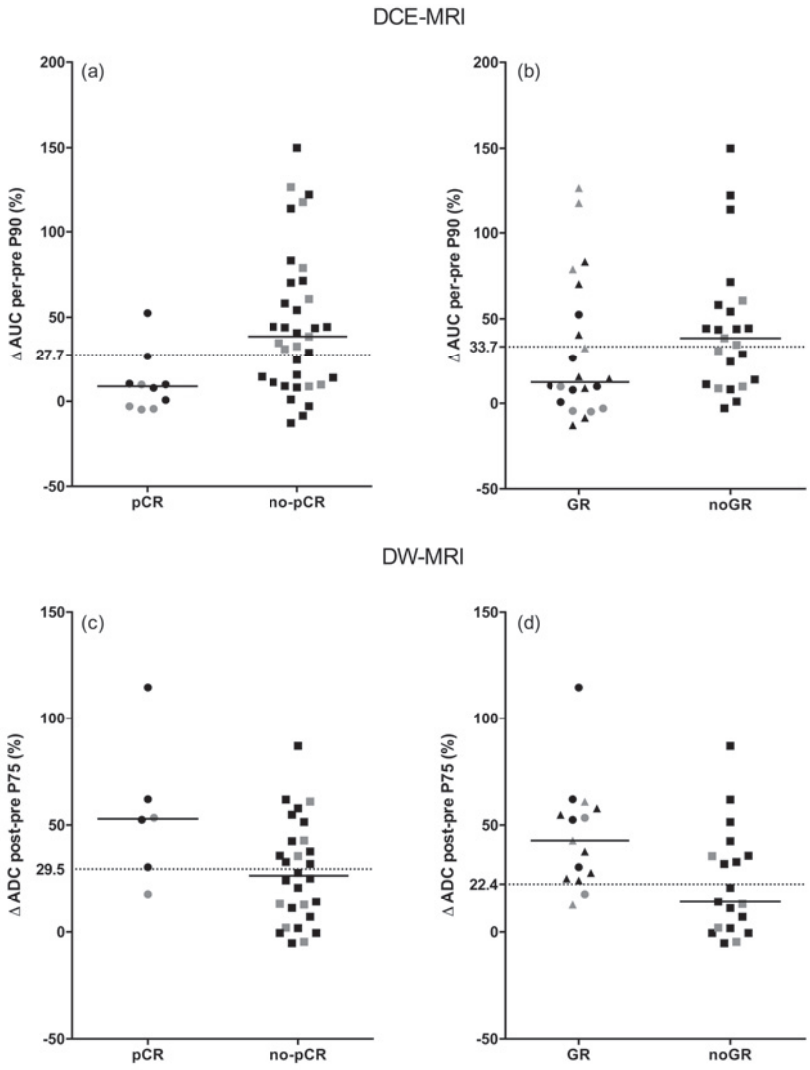

Figure 2. In (a) and (b) 90th percentile (P90) $\Delta AUC_{per\text{-}pre}$ is presented as a function of response and in (c) and (d) 75th percentile (P75) $\Delta ADC_{post\text{-}pre}$. In (a,c) pathologic complete response (pCR) and no-pCR are differentiated while in (b,d) good response (GR) versus poor response is shown. Each dot represents a patient and the two institutes are indicated separately (UMCU in black/NKI in grey). The solid black line for each group represents the median. Threshold lines are indicated for which predictive values are calculated for separation based on response.

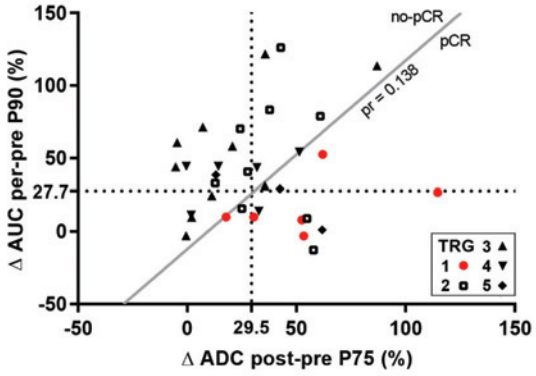

Figure 3. 90th percentile (P90) $\Delta AUC_{per\text{-}pre}$ is plotted as function of 75th percentile (P75) $\Delta ADC_{post\text{-}pre}$. Each dot represents a patient and TRG scores are differentiated using different symbols, with pathologic complete response (pCR) highlighted in red. Equal thresholds from Fig. 2 predicting pCR are indicated in dotted lines. The solid line represents the threshold line (separating pCR from no-pCR) from the multivariable logistic regression model, for which the probability equals 0.138.

DISCUSSION

This multi-center prospective study demonstrates that DW-MRI and DCE-MRI provide complementary information for predicting response to nCRT in patients with esophageal cancer. Separate analysis of both DW-MRI and DCE-MRI showed trends in discriminating good from poor responders comparable to previously published work[17,18].

To our knowledge, this is the first study investigating the complementary value of DW-MRI and DCE-MRI for response prediction in patients with esophageal cancer. A previous published study assessed the independent value of intravoxel incoherent motion (IVIM) MRI and DCE-MRI in patients with esophageal cancer, but did not report a combined analysis[25]. In other tumor sites multiple studies have reported superior descriptive accuracies of combined analyses compared to separate analyses[26,27].

Both DW-MRI and DCE-MRI showed significant associations with response when ADC and AUC were analyzed at separate time points. However, higher c-index values and significant associations with response were found for both modalities when differences between time points were analyzed, which is in correspondence with our previously published work and publications concerning other tumor sites[17,18,28,29]. Compared to predictive values found for ^{18}F-FDG-PET(/CT)[10,11], combining DW-MRI and DCE-MRI reached higher predictive values for response prediction. In the DCE-MRI series, the most predictive parameter was the

difference between the pre-scan and the scan acquired during nCRT. Analyses of DW-MRI series showed, in contrast to previous published work[17], that differences between the post and baseline-scan had a higher predictive value than differences between baseline and per-scans.

Correct prediction of response during treatment may enable early modification of the treatment (i.e. nCRT intensification or discontinuation) while prediction of response using a post-treatment scan can guide the choice to omit surgery and possibly use a wait-and-see approach[30,31].

Combining both modalities increased predictive values and showed that they complement each other (Fig. 3). In this study, uni- and multivariable logistic regression models were used to predict response to nCRT in patients with esophageal cancer. To further optimize the prediction model, the addition of other modalities could be examined, as well as the use of other models (e.g. machine-learning methods)[32,33].

A different approach was chosen for delineation of the tumor compared to our previous work. To minimize inter-observer variability, the pre-scan was delineated using automatic-contouring software[22], which was then transformed to the following time point. Adjustments for possible anatomical changes in esophageal circumference were made using both the ADC-map and anatomical T_2-weighted images. This method is less user-dependent and more sensitive to detect quantitative differences within the tumor over time, because it includes the cranio-caudal length and circumference of the initial tumor on all MR scans. The delineation is thus not solely based on the high b800 signal intensity of each time point separately. This could explain why the $\Delta ADC_{post\text{-}pre}$ was found to be more sensitive to response prediction compared to our previous study[17]. Furthermore, in the current study the DCE-MRI parameter AUC resulted in higher predictive values compared to our previous results, what may be caused by the differences in delineation approaches between this study and our previous smaller DCE-study[18].

In the determination of a threshold for separating responders from non-responders, a trade-off is made between a preference for high specificity (proportion of poor responders well classified), high sensitivity (proportion of good responders well classified), high PPV or high NPV, depending on the purpose. The threshold can be changed to achieve for example a high NPV when the goal is to justify therapy discontinuation in poor responders.

Some limitations apply to this study. First, the reproducibility within patients of the researched parameters is unknown. However, the ADC calculation was validated using a diffusion phantom in both institutes (HPD, Boulder, USA). Second, the exclusion of patients due to poor scan quality resulted in a relatively small sample size of the DW-MRI and multivariable logistic regression analyses, therefore leading to limited clinical impact. Although poor scan quality was found to be patient dependent (i.e. the same patients showed poor scan quality at multiple time points), no relations were found between excluded patients and clinical parameters. After the current study, adjustments to the imaging protocol were made. Promising results were obtained with higher and more stable scan quality and less influence of the presence of breathing motion, which could have possibly influenced the predictive values found in this study. A multicenter prospective validation study in a large cohort of patients is currently underway, which should resolve the limitations in the current literature (ClinicalTrials.gov identifier NCT03474341). The current study justifies inclusion of both modalities, since they showed to be of complementary value. Third, the timing of the second scan was based on our previously published work[11,17,18]. However, a study that is currently being performed in our institute is assessing the optimal time point for response prediction during the course of nCRT, which could further improve the reported predictive values. The timing of surgery was intended to be 6-8 weeks after nCRT with a post-scan within two weeks prior to surgery. Due to logistic reasons this date varied. Variations in time between neoadjuvant therapy and surgery impact the observed pathologic response and could therefore influence our results[34,35].

In conclusion, our multicenter study shows that changes in both DW-MRI and DCE-MRI parameters during treatment are promising imaging markers for prediction of response to nCRT in patients with esophageal cancer. Furthermore, both modalities provide distinct predictive information about the tumor, resulting in increased accuracy when using a multiparametric response prediction model.

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Patient perspectives on repeated MRI and PET/CT examinations during neoadjuvant treatment of esophageal cancer

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ABSTRACT

Objective

The perceived burden of diagnostic tests by patients during the assessment of esophageal cancer warrants attention with the current increase in repeated imaging for purposes of disease monitoring during and after treatment. The purpose of this prospective study was to evaluate the experienced burden associated with repeated MRI and PET/CT examinations during neoadjuvant treatment for esophageal cancer from the perspective of the patient.

Methods

In 27 patients receiving neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer MRI and PET/CT examinations were performed before nCRT, during nCRT and before surgery. The experienced burden during repeated MRI and PET/CT examinations was evaluated with a self-report questionnaire addressing discomfort, pain, anxiety, and embarrassment, each measured on a 5-point Likert scale (1=none; up to 5=very much). In addition, a comparative assessment was used to rank MRI, PET/CT and baseline endoscopy.

Results

All scans were performed without the occurrence of an adverse event. Few patients experienced discomfort (mean score ± SD: 1.9 ± 1.0 for MRI versus 2.0 ± 1.0 for PET/CT, p=0.586), pain (1.1 ± 0.4 for MRI versus 1.3 ± 0.7 for PET/CT, p=0.059), anxiety (1.0 ± 0.2 for MRI versus 1.0 ± 0.2 for PET/CT, p=1.000) and embarrassment (1.0 ± 0 for MRI versus 1.0 ± 0.2 for PET/CT, p=0.317) during both MRI and PET/CT. Patients preferred MRI over PET/CT (67% versus 22%, respectively, p=0.023), and MRI over endoscopy (59% versus 19%, respectively, p=0.027). In the comparison between PET/CT and endoscopy, 59% of patients preferred PET/CT and 26% preferred endoscopy (p=0.093).

Conclusion

Repeated imaging with both MRI and PET/CT is generally well-tolerated for the assessment of response to treatment in esophageal cancer patients. Shorter acquisition times and altered body positioning during scanning will likely improve patient experience.

INTRODUCTION

Esophageal cancer affects more than 450.000 people yearly, and is the sixth most common cause of cancer-related deaths worldwide[1]. Esophageal cancer is currently diagnosed by endoscopy with biopsy combined with multimodality imaging for staging. Since its clinical introduction, whole-body ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with integrated computed tomography (PET/CT) has become an important part of the standard work-up in esophageal cancer staging[2,3]. Currently, high-resolution magnetic resonance imaging (MRI) is emerging as an advanced imaging technique for the staging of different types of cancer, including esophageal cancer[4–8].

In general, diagnostic performance is the main motivation for implementing any diagnostic test, however, acceptability to patients is also an essential consideration. This is particularly relevant in esophageal cancer, given the increase in diagnostic testing for purposes of disease monitoring during and after treatment (e.g. response assessment, restaging, and recurrence detection)[4,9,10]. Patient experience is determined by several elements, including physical discomfort, the risk of side effects due to the investigation, anxiety, embarrassment and diagnostic accuracy[11–14].

Although many reports are available that have assessed the diagnostic ability of different tests in the (re)staging of patients with esophageal cancer, little is known about the perceived burden of these tests by patients. In order to improve patient-friendliness of disease monitoring and (re)staging procedures, it is necessary to evaluate diagnostic procedures from the perspective of the patient. For this reason the imaging community recently emphasized that more research should be performed in this field[15]. Therefore, the purpose of this prospective study was to assess the experienced burden for the patient associated with repeated MRI and PET/CT scanning during preoperative treatment for esophageal cancer, as determined by a questionnaire.

METHODS

Data were collected in a prospective study evaluating the distinct and combined value of MRI (i.e. anatomical as well as functional diffusion-weighted and dynamic contrast enhanced MRI) and PET/CT to predict treatment response to neoadjuvant chemoradiotherapy (nCRT) in patients with esophageal cancer. This prospective study was approved by the institutional review board and written informed consent was provided by all patients. The study was registered with ClinicalTrials.gov, number NCT02125448. The current study concerns an

ancillary study within the prospective study, evaluating the burden of additional MRI and PET/CT examinations using a questionnaire.

Study population

Patients with newly diagnosed biopsy-proven esophageal cancer planned to receive neoadjuvant chemoradiotherapy according to the CROSS regimen[16] followed by surgery were eligible for inclusion. Exclusion criteria included a history of thoracic radiotherapy and contraindications for MRI or PET/CT imaging (NCT02125448).

Diagnostic procedures

Initial diagnostic work-up consisted of endoscopy with biopsy, endoscopic ultrasound, cervical ultrasonography, and an integrated PET/CT for clinical staging. In addition to the initial clinical work-up, patients underwent additional MRI examinations before the start of nCRT, during nCRT after the first 9-15 days (median: 10 days) from the initiation of treatment, and 4-8 weeks (median: 7 weeks) after completion of nCRT but before surgery. Additional PET/CT examinations were performed during nCRT after the first 9-15 days (median: 10 days) from the initiation of treatment, and 4-8 weeks (median: 7 weeks) after completion of nCRT.

Magnetic resonance imaging

Patients underwent MRI scanning with anatomical (T2-weighted) and functional (diffusion-weighted and dynamic contrast-enhanced) MRI sequences. The MRI examinations were performed on a 1.5 Tesla scanner equipped with a 16 or 28-element phased-array receive coil for thoracic imaging (Achieva or Ingenia, Philips Medical Systems, Best, the Netherlands). The MRI scan protocol was specifically developed for esophageal cancer patients[2]. Patients were scanned in supine position with arms parallel to the body without administration of anti-peristaltic agents. Sagittal and transverse T2-weighted images were obtained with a navigator that monitors the position of the diaphragm using a fast 1D-MRI acquisition, in order to trigger scanning exclusively during the end of the expiration[17]. A dynamic contrast-enhanced MRI (DCE-MRI) series was obtained using the contrast agent gadobutrol (Gd-BT-DO3A, Gadovist; Schering AG, Berlin, Germany), injected at a dose of 0.1 mmol/kg of body weight with an automatic syringe pump at a flow rate of 1 mL/s followed by saline injection. All MR images were obtained under free breathing conditions. All participants used the same earplugs (E.A.R. Soft FX; 3M BV) with a reported single number rating of 36dB, combined with headphones. Patients were allowed to select the music they listened to during the MRI examination. The MRI scanning time took approximately 40 minutes per examination.

Positron emission tomography

The ^{18}F-FDG PET scans were performed on a dedicated PET/CT system (mCT, Siemens, Erlangen, Germany). Patients underwent injection of ^{18}F-FDG after fasting for at least six hours. Before injection of FDG, blood glucose levels were checked in every patient to exclude hyperglycemia. The dose of intravenously administered ^{18}F-FDG ranged between 190-370 MBq. Imaging started 60-90 minutes after administration of ^{18}F-FDG with a CT for attenuation correction. The scanning time took approximately 30 minutes per examination. Following CT, PET scanning was performed from thigh to the base of skull in three-dimensional (3D) acquisition mode with 2-5 minutes per bed position. Patients were scanned in radiation treatment position (supine position with arms extended above the head).

Data collection

The experienced burden for the patient associated with the repeated MRI and PET/CT examinations during the clinical work-up was evaluated by means of a questionnaire at the end of the third MRI and PET/CT examination. A questionnaire was handed out after the final tests and patients were requested to complete the questionnaire at that moment. The questionnaire consisted of three modules. First, a standard formatted 5-point Likert scoring module[18] was used to assess items concerning discomfort, pain, anxiety and embarrassment during the examinations that has previously been used in several other imaging studies (Table 1)[11–14]. Second, a comparative module was used, forcing patients to rank different tests (MRI vs. PET-CT vs. conventional staging [i.e. endoscopy]) from least to most inconvenient. Finally, a behavioral intent module was used by asking patients whether or not they, if opportune, would be willing to undergo the specific tests again from a scale of 1 (certainly not) to 5 (certainly yes). Patients were free to write additional comments for each module. The different modules were collated into one comprehensive questionnaire (see Online Supplement 1).

Statistical analysis

The responses of the patients to the different questions for MRI and PET/CT were described as counts with percentages, mean with standard deviation (SD) or median with range as appropriate. Likert scores for MRI and PET/CT were statistically compared using the Wilcoxon signed rank tests in case pairwise comparisons were applicable. For comparison of patient preferences the non-parametric sign test was used. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 23.0 (IBM Corp, Armonk, NY, USA).

TABLE 1. Reported burden scores during MRI and PET/CT scanning for discomfort, pain, anxiety, embarrassment and repeated tests, as well as reported willingness to undergo similar tests in the future

Item	MRI			PET/CT			
	Mean (±SD)	Median	Range	Mean (±SD)	Median	Range	p-value
Discomfort *	1.9 (1.0)	2	1-5	2.0 (1.0)	2	1-5	0.586
Pain *	1.1 (0.4)	1	1-3	1.3 (0.7)	1	1-4	0.059
Anxiety*	1.0 (0.2)	1	1-2	1.0 (0.2)	1	1-2	1.000
Embarrassment *	1.0 (0.0)	1	1	1.0 (0.2)	1	1-2	0.317
Additional burden of tests *	1.3 (0.5)	1	1-3	1.4 (0.6)	1	1-3	0.132
Willingness to undergo similar tests in the future †	4.3 (0.7)	4	3-5	4.2 (0.8)	4	2-5	0.317

*: 1= none; 2= little; 3= quite; 4= very; 5= very much

†: 1= absolutely not; 2= probably not; 3= neutral; 4= probably yes; 5= absolutely yes

RESULTS

Between November 2013 and August 2015, a total of 32 consecutive patients with newly diagnosed esophageal cancer who underwent standard diagnostic work-up signed informed consent. Five patients were excluded from further analyses. Three patients withdrew from study participation, one had unexpected distant metastatic disease during nCRT and did not finish the study, and one did not return the questionnaire. The remaining 27 patients were eligible for further analysis. The study population had a mean age of 63.6 years (SD: 7.6 years), and 23 (85%) of the patients were male. Histologic tumor types included adenocarcinoma (n=21, 78%), squamous cell carcinoma (n=4, 15%) or other types (n=2, 7%). All scans of the 27 patients were performed without the occurrence of an adverse event.

The results of the questionnaires and the difference in MRI and PET/CT are partially demonstrated in Table 2 and Figure 1. Few patients experienced anxiety or embarrassment during MRI and PET/CT scanning, and no statistically significant difference between the tests was observed. With regard to pain, most patients described both MRI (mean: 1.1, SD: 0.4, range: 1-3) and PET/CT (mean: 1.3, SD: 0.7, range: 1-4) as not or little painful, and no significant difference in pain was experienced between the two examinations (p=0.059). In general, patients experienced little discomfort during both MRI (mean 1.9, SD: 1.0, range: 1-5) and PET/CT (mean: 2.0, SD: 1.0, range: 1-5) scanning, and no statistical difference in discomfort was observed between the two examinations (p=0.586). However, a few patients reported high scores of discomfort during either MRI (n=2) or PET/CT (n=2). This was caused by either the position of the body during scanning (MRI n=1, PET/CT n=2) or the noise caused by the MRI scanner (n=1).

When specifically asked what part of the procedure caused the most discomfort (Table 2), patients reported that the main cause of discomfort was the body position in the scanner during MRI (n=6, 22%) and PET/CT (n=14, 52%). The scanning time of both MRI (22%) and PET/CT (15%) was also considered a considerable burden. The necessary waiting time before PET/CT scanning was considered as a burden by 5 (19%) of the 27 patients. The noise caused by the MRI scans was indicated to be unpleasant by 7 (26%) of the patients. Only a small number of patients considered the insertion of the intravenous line (MRI: n=1, PET/CT: n=1) or being in a small room during the tests (MRI: n=1, PET/CT: n=1) as a cause of discomfort. One patient noted that fasting for at least six hours prior to the PET/CT examination had been very uncomfortable while losing weight due to disease and treatment burden. Another patient reported that it could get uncomfortably warm inside the MR scanner during the scanning.

In the comparative module patients were asked to rank different tests regarding comfort (Figure 2). Eighteen out of 27 patients (67%) preferred MRI over PET/CT, 6 (22%) preferred PET/CT over MRI, and 3 (11%) did not express a preference (p=0.023). In the comparison between PET/CT and endoscopy, 16 (59%) patients preferred PET/CT, 7 (26%) endoscopy and 4 (15%) did not express a preference(p=0.093). When asked to choose between MRI and endoscopy, 16 (59%) patients preferred MRI, 5 (19%) endoscopy and 6 (22%) did not express a preference (p=0.027).Characeteristics of the three diagnostic tests are presented in Table 3.

Overall the additional burden of the MRI (mean: 1.3, SD: 0.5, range: 1-3) or PET/CT (mean: 1.4, SD: 0.6, range 1-3) on top of treatment and other diagnostic procedures was regarded as being acceptable and comparable between the two modalities (p=0.132). When patients were asked whether or not they, if opportune, would be willing to undergo the MRI or PET/CT scans again, most answered ‘probably yes’ ([mean: 4.3, SD: 0.7, range: 3-5] versus [mean: 4.2, SD: 0.8, range: 2-5], p=0.317, respectively). Some patients noted that it gave them a good feeling being able to contribute to scientific research (n=2).

TABLE 2. Part of test procedure that caused most discomfort

Item	MRI		PET/CT	
	n	%	n	%
Most stressful part of test				
-Insertion of intravenous line	1	4	1	4
-Insertion of contrast (or FDG)	0	0	0	0
-Waiting time before scanning	NA	NA	5	19
-Scan time	6	22	4	15
-Body position in the scanner	6	22	14	52
-Noise of the scanner	7	26	0	0
-Being in a small room	1	4	1	4
-Non specifically	6	22	2	7

NA: not applicable

TABLE 3. Characteristics of the three diagnostic tests

Procedure	**Fasting**	**IV line**	**Sedation**	**Pharmaceutical**	**Duration (min)**
MRI	No	Yes	No	Gadobutrol (Gadovist)	≈ 30
PET/CT	Yes	Yes	No	^{18}F-FDG	≈ 90-120 (of which 30 minutes actual scanning time)
Endoscopy	Yes	Yes*	Yes*	Midazolam*	≈ 45

IV: intravenous; *: optional

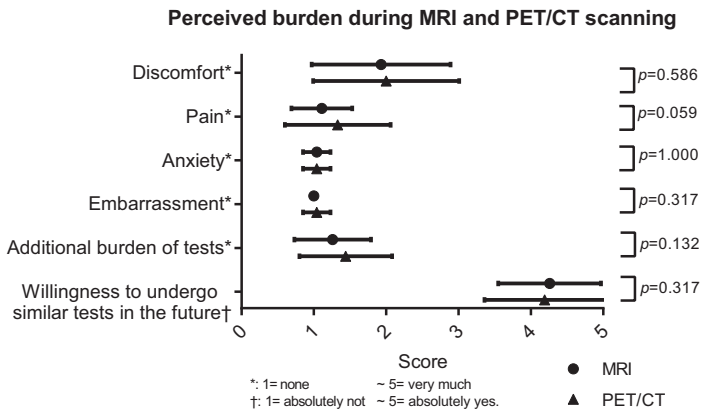

Figure 1. Perceived burden by the patients during MRI and PET/CT scanning.

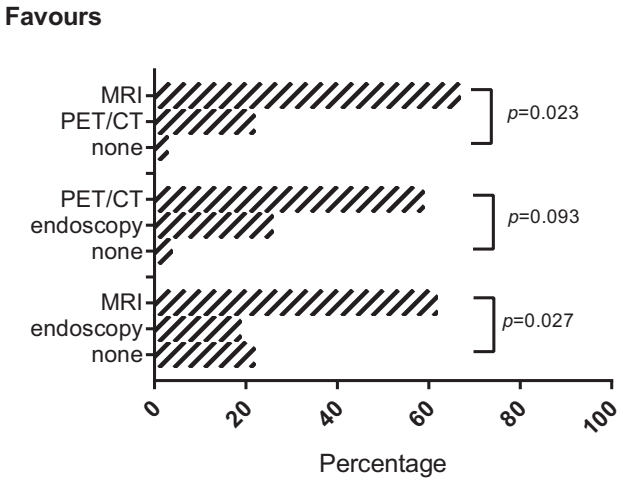

Figure 2. Comparative module forcing patients to rank the different tests from least to most inconvenient.

DISCUSSION

In this single center prospective study, patient experience of repeated MRI and PET/CT scanning during preoperative treatment for esophageal cancer was evaluated. The results of the current study show that patients experience MRI and PET/CT scans on top of treatment and other diagnostic examinations as a reasonable burden. When asked to rank the different tests, patients preferred MRI over PET/CT and endoscopy.

Several studies have shown that MRI is a feasible technique in esophageal cancer imaging, and is a promising tool for response to treatment assessment[4,6–8]. Especially due to the unsatisfactory results in treatment response assessment of conventional diagnostic techniques (i.e. endoscopic ultrasonography[19], endoscopy with biopsy[19], and PET/CT[20–22]), the results of MRI for response assessment in esophageal cancer is currently of high clinical interest. From a patient perspective, the acceptable experience of MRI imaging in the current study supports its further utilization in clinical practice. Also, it is reassuring that patients find the additional burden of MRI and PET/CT examinations – on top of treatment and other diagnostic studies – acceptable, given the increase in repeated diagnostic examinations over the course of treatment and follow-up in esophageal cancer[2,4,5].

Although the results of the current study indicate a slight overall patient preference of MRI over PET/CT, a large range of determinants influenced patient preferences with clear interindividual differences. The assumption, therefore, that MRI is better tolerated and preferred to PET/CT by

all patients would not be valid. Patients place different personal weightings on the importance of test characteristics, which in turn influences overall test preference. However, the results of the current study do indicate actions that could improve patient experience during either MRI or PET/CT imaging. First, the fact that body position, the need to lie still, and duration of scanning were the main causes for discomfort during both MRI and PET/CT acquisition indicates that a more comfortable position and faster scanning may improve the acceptance of both MRI and PET/CT imaging. Second, the noise caused by the MRI scans was indicated to be unpleasant by 7 (26%) of the 27 patients. Although earplugs combined with headphones with patient's preferred music were available, this was apparently not sufficient to reduce the noise to an acceptable level for all patients. The intrusive nature of the MRI scanner noise – despite measures to reduce the noise levels – has been previously noted by several studies assessing patient perception of MRI[23,24]. To this regard, more noise reduction than provided in the current study should be made available, which may be a simple measure to improve patient perception. Third, careful patient preparation, including detailed verbal information and recognition for patients' emotions during the imaging exam, will likely improve patient compliance required for recording adequate images[25].

Against the common expectation that the least invasive diagnostic test would have the patients' preference, 5 (19%) and 7 (26%) of the patients preferred endoscopy over MRI and PET/CT, respectively. These findings are most likely caused by the difference in administration of sedation and the timing of measurement of patient preferences between the examinations. In contrast to MRI and PET/CT, sedatives were administered to most patients during endoscopy which has shown to improve the acceptance of gastrointestinal endoscopy[26]. Furthermore, the questionnaire administration was directly performed after the last MRI and PET/CT examination, while the last endoscopy was performed 10 to 15 weeks prior to the questionnaire. This difference in timing may have influenced patient experience of endoscopy over time[27]. In future endeavors to compare patient preferences between endoscopy and imaging modalities, these factors should be taken into account in the study design.

Several limitations of the current study must be considered. First, patients did not receive information on the diagnostic performance of MRI and PET/CT for the assessment of response to treatment in esophageal cancer. Previous studies on patient perception of diagnostic modalities, however, have shown that diagnostic performance is a major aspect of overall patient preference[28]. Second, it has been indicated that patients that volunteer to participate in prospective research are likely different from the initial target populations[29]. In that regard, the burden of the additional scans may be underestimated by the current study, as patients who

were informed about the study and found the additional scans too burdensome have probably refused to participate. Third, all MRI scans were acquired directly after PET/CT acquisition, which may have biased the results when considering the total duration of both procedures combined. Furthermore, MRI is a developing technique in the field of esophageal cancer imaging, with a multitude of available different acquisition protocols. Some of these protocols require intravenous contrast injection and they all have a specific sound level. Our results may therefore not be directly generalizable to other MRI acquisition techniques.

In conclusion, this study indicates that repeated imaging with both MRI and PET/CT is generally well-tolerated for the assessment of response to treatment in esophageal cancer patients. Shorter acquisition times and altered body positioning during scanning will likely improve patient experience during MRI and PET/CT acquisition.

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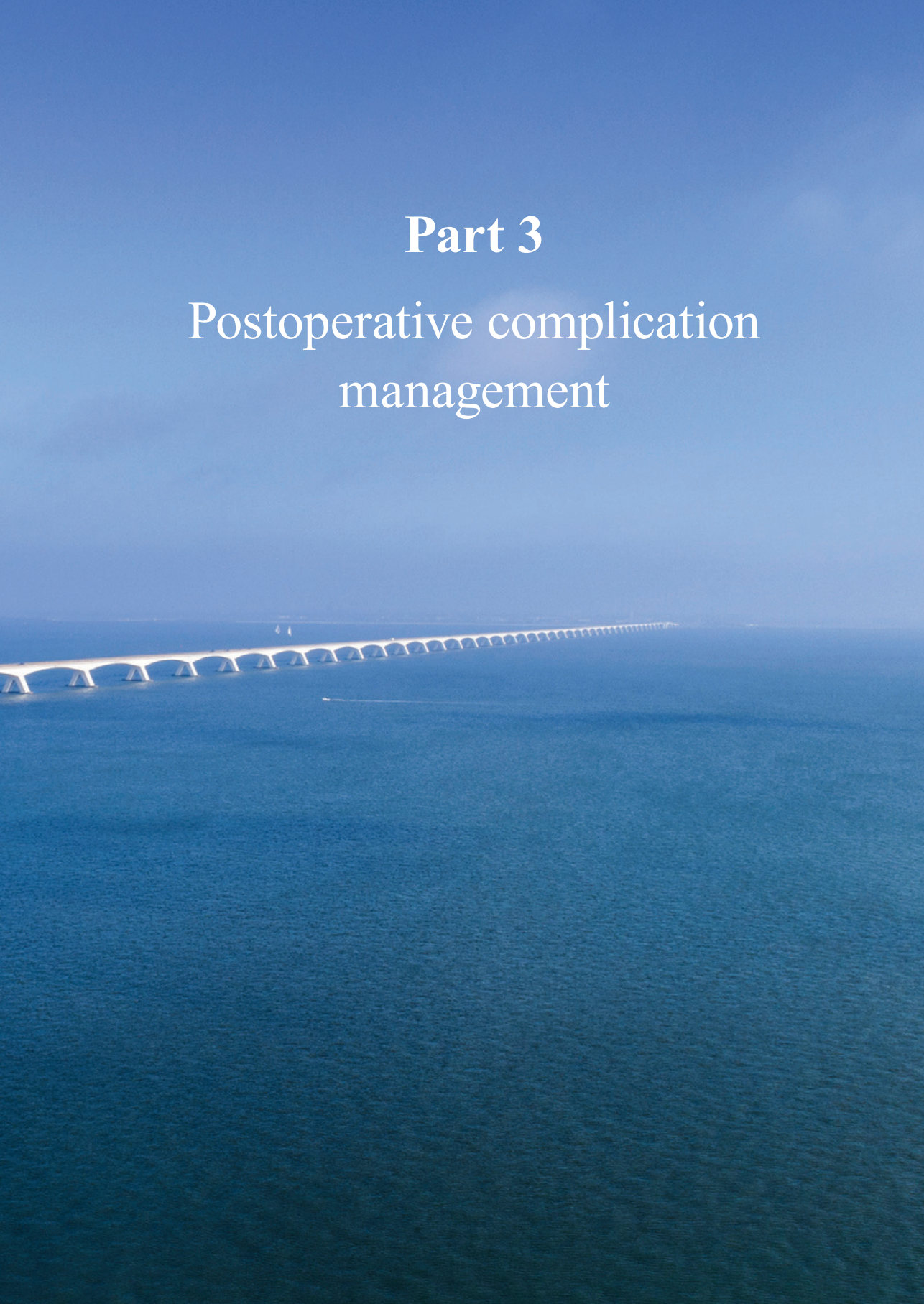

Part 3

Postoperative complication management

11

Hospital costs of complications after esophagectomy for cancer

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ABSTRACT

Objective

The purpose of this study was to estimate the economic burden of postoperative complications after esophagectomy for cancer, in order to optimally allocate resources for quality improvement initiatives in the future.

Methods

A retrospective analysis of prospectively collected clinical and financial outcomes after esophageal cancer surgery in a tertiary referral center in the Netherlands was performed. Data was extracted from consecutive patients registered in the Dutch Upper GI Cancer Audit between 2011 and 2014 (n=201). Costs were measured up to 90-days after hospital discharge and based on Time-Driven Activity-Based Costing. The additional costs were estimated using multiple linear regression models.

Results

The average total cost for one patient after esophagectomy was €37,581 (±31,372). The estimated costs of an esophagectomy without complications were €23,476 (±6,496). Mean costs after minor (47%) and severe complications (29%) were €31,529 (±23,359) and €59,167 (±42,615) ($p<0.001$), respectively. The 5% most expensive patients were responsible for 20.3% of the total hospital costs assessed in this study. Patient characteristics associated with additional costs in multivariable analysis included, age >70 (+€2,922, $p=0.036$), female gender (+€4,357, $p=0.005$), COPD (+€5,415, $p=0.002$), and a history of thromboembolic events (+€6,213, $p=0.028$). Complications associated with a significant increase in costs in multivariable analysis included anastomotic leakage (+€4,123, $p=0.008$), cardiac complications (+€5,711, $p=0.003$), chyle leakage (+€6,188, $p<0.001$) and postoperative bleeding (+€31,567, $p<0.001$).

Conclusion

Complications and severity of complications after esophageal surgery are associated with a substantial increase in costs. Although not all postoperative complications can be prevented, implementation of preventive measures to reduce complications could result in a considerable cost reduction and quality improvement.

INTRODUCTION

Esophageal cancer is the sixth leading cause of death from cancer worldwide and the incidence rate has been rising over the past decades[1]. In case of localized non-metastatic esophageal cancer, surgical resection of the esophagus with en-bloc lymphadenectomy combined with induction therapy is the recommended treatment strategy[2-4]. Survival following esophageal resection for cancer has improved considerably over the past decades due to advances in surgical treatment and perioperative care[5]. Despite these recent developments, up to 74% of the patients still experience a complicated course after this complex surgical procedure[6].

The current increase in health care expenses worldwide has encouraged healthcare providers to place emphasis on both improving quality of (cancer) care and reducing costs[7,8]. It is well recognized that complications after esophageal surgery are associated with increased length of hospital stay, long-term morbidity and mortality[9]. Recent studies analyzing hospital costs after (complex) surgical procedures indicate that postoperative complications are associated with increased resource utilization[10, 11]. Such results may appear somewhat expected, however, detailed data regarding the clinical and economic burden of postoperative complications, independent of other baseline co-morbidities, particularly after esophagectomy, remains limited. A clear understanding of the clinical and economic impact of postoperative complications after esophagectomy would allow development of further quality improvement and cost-reduction initiatives, which may improve patient outcomes and reduce hospital costs in an era when cost-reduction is at the foreground of healthcare initiatives.

Therefore, the purpose of this study was to evaluate the economic burden of postoperative complications after esophagectomy, in order to optimally allocate resources for quality improvement initiatives in the future.

METHODS

Study population

Institutional review board approval was obtained and the requirement for written informed consent was waived for this study. All consecutive patients who underwent an elective esophagectomy for esophageal or gastro-esophageal junction cancer, between January 1st 2011 and December 31st 2014, at our tertiary referral center were prospectively registered in the Dutch Upper GI Cancer Audit (DUCA) and included for analysis[12]. Surgical treatment consisted of transthoracic or transhiatal esophagectomy with en-bloc lymphadenectomy followed by gastric tube reconstruction with cervical anastomosis end-to-side with hand-sewn continuous sutures in monolayer[13].

Data collection

Patient and treatment-related characteristics were extracted from the prospectively maintained database (Table 1). Patient and treatment-related parameters included gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, type of surgery (i.e. open or minimally invasive), surgical approach (i.e. transhiatal or transthoracic resection), chronic obstructive pulmonary disease (COPD), cardiac comorbidity, vascular comorbidity, any comorbidity, diabetes mellitus, and neoadjuvant treatment. Definitions of the different comorbidities are presented in Table 1. All clinical outcomes during admission or readmissions after surgery were prospectively registered in the DUCA. Postoperative complications included anastomotic leakage, pneumonia, wound infection, postoperative bleeding, cardiac complications, chyle leakage, thromboembolic events, and recurrent laryngeal nerve paresis. Definitions of the reported complications are presented in Table 1. The severity of postoperative complications were classified as either minor (equal to Clavien-Dindo grade I, II, IIIa) or major complications (Clavien-Dindo grade IIIb, IV or V)[14, 15]. In case of multiple complications in one patient, the level of severity of the most severe complication was decisive. Patients without a minor or severe complication were classified as 'no complication'.

Cost analysis

The cost analysis was conducted from a hospital perspective. Therefore, only 'in-hospital' costs were assessed from the day of primary surgery until discharge, and 90 days thereafter. Resource utilization at patient level (e.g. laboratory costs, operation room time, ward days, use of laparoscopic instruments) was extracted from the hospital information system, and translated into costs by Performation (Bilthoven, The Netherlands), which is a healthcare consultancy firm providing patient level costing. Time-Driven Activity-Based Costing (TD-ABC) methodology was used to calculate costs, which is an advanced method for understanding hospitals costs[16]. In all activities, direct (e.g. personnel staff, material and equipment) and indirect costs (e.g. cleaning, catering, and utilization of the hospital building) were incorporated. The hospital specific Patient Identification Number was used to match DUCA registered patients to the financial database. Four (2%) patients without a match were excluded from analyses.

Statistical analysis

Descriptive analysis of patient and treatment-related characteristics, and postoperative complications were performed using summary statistics. The association of patient and treatment-related characteristics and complications was studied univariably. Continuous variables were summarized as mean with standard deviation (SD) or median with interquartile range, and categorical variables were presented as frequencies with percentages. Categorical parameters were compared using the Chi-square test or Fisher's exact test in case of small cell counts. The Student's T-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous parameters, respectively.

The association of patient and treatment-related characteristics and complications with total costs was studied using univariable and multivariable linear regression. Regression models were constructed providing regression coefficients with 95% confidence intervals (CIs) and *p*-values. Logarithmic transformation was applied of the dependent variable (total costs) because of its non-linear distribution. Possible predictors were entered in the multivariable analysis when showing a near significant (i.e. $p \leq 0.10$) difference in costs according to the univariable linear regression analysis. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY). A *p*-value of <0.05 was considered statistically significant.

RESULTS

In the study period a total of 201 patients underwent esophagectomy with gastric tube reconstruction. The study population was predominantly male (76%), had a mean age of 67 years, and 70% had any form of comorbidity. In the studied population 79% underwent a transthoracic approach.

The average cost per patient was €37,581 (±31,372), ranging from €12,332 (least expensive 2.5%) to €179,555 (most expensive 2.5%). The 5% most expensive patients were responsible for 20.3% of the total hospital costs assessed in this study (Figure 1). Unadjusted associations of patient and treatment-related characteristics with hospital costs are presented in Table 1. Patient characteristics associated with additional costs in univariable analysis included female gender, age >70, higher ASA scores, vascular comorbidity and COPD. Other studied patient and treatment-related factors (e.g. type of surgery and the use of induction therapy) were not significantly associated with increased postoperative hospital costs.

Postoperative complications

Overall, 154 (76%) patients experienced at least one complication. Patients with one or more complications had a longer postoperative length of hospital stay (median 11 [range 8-21] versus 19 days [range 9-124, p<0.001]), and a higher 90-day mortality (0% vs. 5.6%, p=0.118), compared to patients without a complication. The estimated costs of a patient without complications was €23,476 (± 6,496), compared to €31,529 (±23,359) and €59,167 (±42,615) for patients with minor and major complications, respectively (Figure 1). In univariable linear regression minor complications were associated with a significant increase in costs of €5,093 (95%CI: €1,065-9,806, p<0.001). The overall increment in costs after minor complications was caused in particular by higher costs in ward care and intensive care (Table 2). Using univariable linear regression severe complications were significantly associated with an increase in costs of €26,934 (95%CI: €19,060-36,294, p<0.001). The additional costs of severe complications accounted for 27% of the total hospital costs. The overall increment in costs for severe complications was caused in particular by higher costs for intensive care, ward care, blood products and use of laboratory and radiology (Table 2).

Unadjusted associations of specific complications with hospital costs are presented in Table 1. Complications associated with additional costs in univariable analysis included anastomotic leakage, chyle leakage, cardiac complications and postoperative bleeding. Other studied complications were not significantly associated with increased hospital costs. Higher severity grades of the most common complications (i.e. pneumonia, anastomotic leakage, chyle leakage, and cardiac complications) were associated with an increase in both hospital costs and length of hospital stay after esophagetomy (Table 3). For example, the average costs of patients with a pneumonia defined as a 'major complication' were 112% higher (€65,851) as compared to patients with a pneumonia defined as 'minor complication' (€31,058).

Adjusted analysis of factors associated with hospital costs

Patient and treatment-related characteristics, and complications that showed a potential association with hospital costs in univariable analysis ($p \leq 0.10$) were selected for multivariable linear regression analysis using the logarithm of the total costs (Table 4). Patient related factors that remained independently associated with an increase in hospital costs included age >70 (€2,922, p=0.036), female gender (€4,357, p=0.005), COPD (€5,415, p=0.002), and a history of thromboembolic events (€6,213, p=0.028). Complications that remained independently associated in multivariable analysis included anastomotic leakage (€4,123, p=0.008), cardiac complications (€5,711, p=0.003), chyle leakage (€6,188, p<0.001), and postoperative bleeding (31,567, p<0.001).

TABLE 1. Analysis of postoperative hospital costs (in Euros) for patient, treatment-related characteristics and postoperative complications after esophagectomy

Characteristic	n (%)	Average costs*	*p* value
No. of patients	201 (100)	37,581 ± 31,372	
Gender			0.014
Male	150 (75.6)	34,823 ± 26,579	
Female	51 (25.4)	45,693 ± 41,733	
Age at time of surgery			<0.001
<70 Years	117 (58.2)	31,126 ± 16,182	
>70 years	84 (41.8)	46,572 ± 43,187	
Body mass index			0.388
<30 kg/m^2	174 (86.6)	38,470 ± 33,134	
>30 kg/m^2	27 (13.4)	31,849 ± 15,049	
ASA score			0.003
I	43 (21.4)	29,382 ± 16,057	
II	123 (61.2)	37,890 ± 33,813	
III	35 (17.4)	46,570 ± 34,642	
Cardiac co-morbidity†			0.330
No	148 (71.1)	36,361 ± 29,392	
Yes	53 (28.9)	40,987 ± 36,431	
Vascular co-morbidity‡			0.023
No	125 (62.2)	34,511 ± 27,223	
Yes	76 (37.8)	42,629 ± 36,848	
Diabetes mellitus			0.528
No	173 (86.1)	37,758 ± 32,948	
Yes	28 (13.9)	36,486 ± 19,326	
COPD			<0.001
No	160 (80.1)	33,991 ± 29,218	
Yes	41 (19.9)	51,590 ± 35,717	
History of thromboembolic events			0.072
No	188 (93.5)	36,394 ± 27,403	
Yes	13 (7.5)	54,737 ± 66,033	
Urological co-morbidity			0.161
No	182 (90.5)	36,984 ± 31,770	
Yes	19 (9.5)	27,361 ± 27,360	
Any co-morbidity			<0.001
No	60 (29.9)	27,375 ± 12,108	
Yes	141 (70.1)	41,923 ± 35,785	
Surgical approach			0.876
Transhiatal	42 (20.9)	36,275 ± 23,407	
Transthoracic	159 (79.1)	37,926 ± 33,213	

TABLE 1 (continued). Analysis of postoperative hospital costs (in Euros) for patient, treatment-related characteristics and postoperative complications after esophagectomy

Characteristic	n (%)	Average costs*	*p* value
Neoadjuvant therapy			0.862
No therapy	37 (18.4)	38,109 ± 29,722	
Chemotherapy	55 (27.4)	38,945 ± 36,854	
Chemoradiotherapy	109 (54.2)	36,713 ± 29,108	
Complications			
Complication grade			<0.001
No complication	48 (23.9)	23,476 ± 6,496	
Minor complications	95 (47.3)	31,529 ± 23,359	
Major complication	58 (28.8)	59,167 ± 42,615	
Pneumonia[§]			0.098
No	123 (61.2)	35,777 ± 33,702	
Yes	78 (38.8)	40,426 ± 27,264	
Anastomotic leakage‖			0.001
No	147 (73.1)	35,125 ± 31,355	
Yes	54 (26.9)	44,268 ± 30,716	
Chyle leakage[#]			<0.001
No	165 (82.1)	34,446 ± 25,919	
Yes	36 (17.9)	51,949 ± 47,090	
Cardiac complications[¶]			0.004
No	171 (85.1)	35,995 ± 31,790	
Yes	30 (14.9)	46,618 ± 27,643	
Wound infection			0.936
No	184 (91.5)	37,817 ± 32,295	
Yes	17 (8.5)	35,015 ± 19,121	
Laryngeal nerve paresis			0.463
No	188 (93.5)	36,756 ± 27,421	
Yes	13 (6.5)	49,501 ± 67,238	
Postoperative bleeding			<0.001
No	196 (97.5)	35,982 ± 29,458	
Yes	5 (2.5)	100,232 ± 43,297	
Thromboembolic event			0.779
No	196 (97.5)	37,531 ± 31,484	
Yes	5 (2.5)	39,503 ± 29,713	

Data presented as numbers of patients with percentages in parentheses. *Data presented as mean ± standard deviation. [†]Any record of historical treatment of any cardiac disorder at a cardiology department. [ǂ]History of hypertension or peripheral vascular disease requiring vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding vein stripping) or documented aortic aneurysm with or without repair. [§]Pneumonia was defined by the universal pneumonia score[36].‖Anastomotic leakage included all clinical and radiological findings of anastomotic dehiscence or fistula.[#]Chyle leak was defined as elevated levels of triglycerides in intrathoracic fluid requiring treatment. [¶]Any new cardiac disorder requiring direct treatment (e.g. cardiac arrhythmia). Data presented as median with interquartile range [IQR] between brackets.

TABLE 2. Detailed analysis of costs for patients without and with minor or major complications

	No complication	minor complications	major complications
Surgical costs	5,374	5,239	5,552
Other interventions	1,569	1,901	2,542
Ward care	8,524	11,734	19,008
Intensive care	2,524	5,101	18,860
Laboratory costs	1,974	2,518	5,048
Radiology	1,164	1,480	2,577
Other diagnostics	301	410	579
Blood products	103	272	2,126
Outpatient clinic	1,316	1,438	1,215
Other	627	1,436	1,660
Total	23,476	31,529	59,167**

** Difference in total costs was statistically significant ($p<0.001$)

TABLE 3. Univariable cost analysis of complications according to severity

	Total group n	Costs (€)*	Median length of stay in days
Complication grade			
No complication	48	23,476	11
Minor complication	95	31,529	15
Major complication	58	59,167	35
Total	201	37,581	16
Anastomotic leakage			
Minor complication	25	43,292	20
Major complication	29	45,108	29
Total	54	44,268	26.5
Pneumonia			
Minor complication	57	31,058	17
Major complication	21	65,851	39
Total	78	40,425	20
Chyle leakage			
Minor complication	29	39,858	14
Major complication	7	102,040	35
Total	36	51,949	26
Cardiac complications			
Minor complication	28	44,943	25
Major complication	2	70,080	38
Total	30	46,618	25.5

*Costs are represented in Euros (€).

TABLE 4. Multivariable analysis of factors potentially associated (*p ≤0.10)* with postoperative hospital costs after esophagectomy*

Characteristic	***B*[#] (95%CI)**	**Attributable costs (€)***	***p* value**
Gender			
Male	Reference		
Female	0.205 (0.061-0.349)	4,357	0.005
Age at time of surgery			
<70 Years	Reference		
>70 years	0.142 (0.100-0.274)	2,922	0.036
ASA score			
I	Reference		
II	0.093 (-0.710-0.257)	1,866	0.265
III	0.126 (-0.870-0.338)	2,571	0.246
Vascular co-morbidity	0.083 (-0.048-0.213)	1,657	0.214
Pulmonary co-morbidity	0.249 (0.091-0.407)	5,415	0.002
History of thromboembolic events	0.281 (0.030-0.532)	6,213	0.028
Complications			
Pneumonia	0.087 (-0.041-0.214)	1,741	0.184
Anastomotic leakage	0.195 (0.052-0.339)	4,123	0.008
Chyle leakage	0.280 (0.115-0.446)	6,188	<0.001
Cardiac complications	0.261 (0.087-0.436)	5,711	0.003
Postoperative bleeding	0.974 (0.573-1.376)	31,567	<0.001

* Adjusted for patient and treatment-related characteristics (i.e. gender, age, ASA score, vascular co-morbidity, pulmonary co-morbidity, history of thromboembolic events) and complications (i.e. pneumonia, anastomotic leakage, chyle leakage, cardiac complications, postoperative bleeding) potentially associated with postoperative hospital costs (≤0.10). [#] Intercept *B* = 9.860 (19,149 euro)

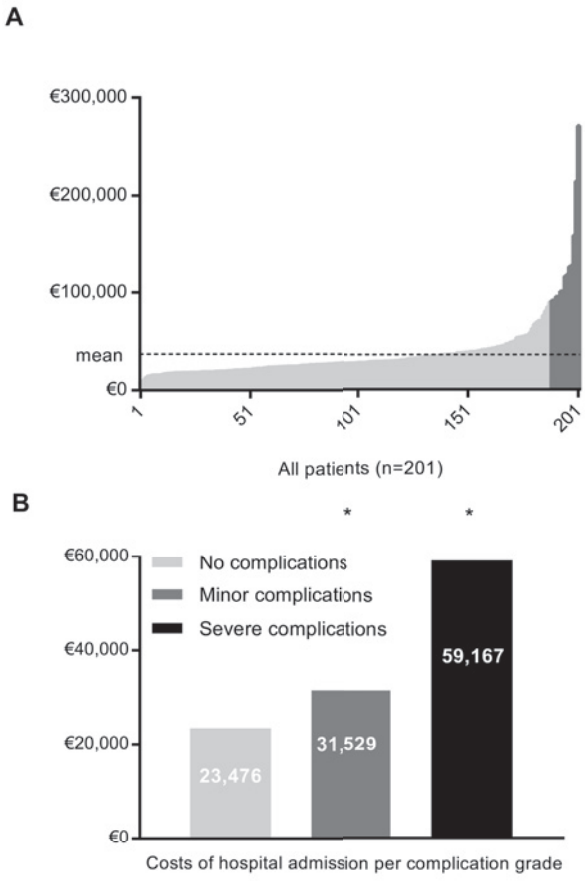

Figure 1. A: Figure shows the distribution of costs of patients after esophagectomy for cancer. Each bar represents the cost of a patients. The 5% most expensive patients (Dark gray bars) were responsible for 20.3% of the total hospital costs in this study. **B:** Figure illustrates the increase in costs for patients with minor and severe complications, respectively. (*Variables significantly associated with higher hospital costs).

DISCUSSION

This study demonstrates that postoperative complications after esophagectomy are common, and associated with worse clinical outcomes and higher costs. Not only the type of complication (e.g. anastomotic leakage) but also the severity of complications was associated with higher costs. In particular, additional costs of severe complications accounted for 27% of the total hospital costs. The results of this study emphasizes the need for detailed cost information

of (surgical) treatments in order to optimally allocate resources for quality improvement initiatives in the future.

Postoperative complications

In-hospital mortality occurred in 4% of the patients in this study, which is lower than large population-based registries (between 6% and 9%)[17,18], and emphasizes that despite its complexity esophagectomy can be safely performed in a high volume center. However, 29% of patients experienced major complications requiring reintervention, accounting for a significant increase in total hospital costs. This increase in costs is similar to other studies analyzing gastro-intestinal surgical procedures (i.e. liver, pancreas gastric, bypass and colorectal surgery) that also found an increase in hospital costs in case of major complications [19-21].

Complications that were independently contributing to higher costs after esophagectomy in the current analysis included anastomotic leakage, chyle leakage, cardiac complications and postoperative bleeding (Table 4). As the incidence of each complication is different, the attribution to the total hospital costs was highest for the complications with a high incidence (i.e. anastomotic leakage [incidence rate: 27%], chyle leakage [incidence rate: 18%] and cardiac complications [incidence rate: 15%]). These findings correspond with the results of a previous study that identified anastomotic leakage as independent attributor to increased hospital costs, and chyle leakage as the complication that incurred the greatest costs after esophagectomy[22]. Although not all (surgical) complications can be prevented, the results of the current study suggest that efforts focusing on reducing the incidence of these specific postoperative complications may hold the potential to improve clinical outcomes and minimize hospital costs[22].

In our current study, pneumonia was the most frequently reported complication after esophagectomy, yet the occurrence of pneumonia alone was not independently associated with an increase in hospital costs. However, a clear trend was visible to higher hospital costs for patients diagnosed with pneumonia resulting in respiratory failure and sepsis requiring prolonged ventilator support, increasing the mean costs per patient by a factor 2 (Table 3). Therefore, the prevention of invasive procedures or organ system failure due to pneumonia is obviously crucial. This is supported by a previous study that did not identify pneumonia as independent contributor to increased hospital costs, but did report an increase in costs and length of hospital stay for patients with respiratory failure due to pneumonia[22]. These results underline the importance of recording complications by severity, and not only as binary occurrences (i.e. yes or no)[14,15,20].

The current study did not identify any difference in costs between a transthoracic and a transhiatal approach. In literature a transhiatal approach has been associated with a shorter length of hospital stay and less postoperative morbidity by averting a thoracotomy[23]. Therefore, the transhiatal approach has been associated with lower hospital costs as compared to a transthoracic approach[24]. However, in the current study only patients with severe cardiopulmonary co-morbidity were scheduled for a transhiatal esophagectomy, as the risk of complications associated with single lung ventilation during transthoracic resection was considered too high. Although the initial surgical costs were €2077 lower for patients treated with transhiatal esophagectomy, they had a longer length of hospital stay (18 versus 15 days) due to their poor comorbidity status. This has likely resulted in the equal distribution of costs between the two approaches. However, the current study was not designed - and hence does not allow - to answer the question whether surgical approach per se is associated with hospital costs, but rather to determine costs of complications independent of treatment and patient-related factors.

Patient characteristics

Analysis of patient demographics demonstrated that a substantial number of patients presenting for esophageal surgery had considerable comorbidities, which was similar to the findings of a large study which analyzed demographic characteristics of patients undergoing esophagectomy[25]. The importance of preoperative management of comorbidities is demonstrated by the observation that several of the patient characteristics (e.g. older patients, COPD, and a history of thromboembolic events) were independent predictors for higher costs after esophagectomy. This is also suggested by a previous study demonstrating that preoperative risk factors are equally important as complications for the prediction of hospital costs after surgery[26].

Patient-related characteristics may influence hospital costs in different ways. Patients with comorbidities could have a longer hospital stay or be more expensive to treat, regardless whether a postoperative complication occurred[26]. Hospitalization of anticoagulant-treated patients with a history of thromboembolic events, for example, results in higher hospital costs compared to other patients. These findings suggest that optimizing the preoperative physical state of patients could result in cost savings and quality improvement.

Understanding the costs associated with complications may provide the business case for complication-specific quality improvement programs. These programs should not only aim to reduce the incidence of complications but also focus on reducing severity of complications, as

hospital costs mainly depend on severe complications resulting in a longer length of hospital stay. Proposed opportunities to improve the preoperative physical state of patients include physical therapy to increase cardiorespiratory function[27,28], improve nutritional status[29,30], and preoperative optimization of oxygen delivery[31]. Moreover, effective pain management that enables fast postoperative mobilization has an important role in recovery after esophagectomy. Previous studies have suggested that paravertebral and thoracic epidural analgesia after thoracotomy may provide sufficient pain relief and result in a lower risk of pneumonia[32]. Also, preoperative ischemic conditioning of the stomach may reduce the risk of anastomotic leakage after esophagectomy in a selected group of patients[33, 34]. However, further studies are needed to elucidate which interventions may result in a lower incidence of complications and reduce costs after esophagectomy.

Strengths and limitations

The financial data used in this study represents the actual patient-specific costs of hospitalization using TD-ABC methodology, rather than using proxies of costs from insurance claims or hospital records[16]. As a result, a detailed overview of costs for every aspect of a patient's hospitalization was available. As shown in Table 2, for instance, the overall increment in costs associated with severe complications depended in particular on ward care and intensive care. These methods have previously been used to link clinical outcomes after colorectal surgery (from the Dutch Surgical Colorectal Audit) with direct costs from all 29 participating hospitals [19, 35]. This methodology is important as it provides relevant information about the relation between quality and costs of care in an efficient manner.

A few study limitations warrant attention. First, this study was based on single center data. Therefore its limitations, especially regarding external validity, should be acknowledged, as it is well known that complications rates and hospital costs may vary between hospitals. Second, costs were analyzed from a hospital perspective and did not extend beyond the in-hospital costs up to 90 days after discharge. Consequently, costs such as outpatient care and loss of income have not been assessed.

In conclusion, this study demonstrates that complications and severity of complications after esophagectomy are associated with a substantial increase in hospital costs. Anastomotic leakage and chyle leakage resulted in the largest additional costs. Although not all postoperative complications can be prevented, implementation of preventive measures to reduce complications could result in quality improvement and a considerable cost reduction.

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Impact of postoperative complications on outcomes after oesophagectomy for cancer

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ABSTRACT

Objective

In order to optimally allocate healthcare resources, complication-related quality initiatives should target those complications that have the greatest overall impact on outcomes after surgery. The aim of this study was to identify the most clinically relevant complications following oesophagectomy for cancer in a nationwide cohort study.

Methods

Consecutive patients who underwent oesophagectomy for cancer between January 2011 and December 2016 were identified from the Dutch Upper Gastrointestinal Cancer Audit. The adjusted population attributable fraction (PAF) was used to estimate the impact of specific postoperative complications on the clinical outcomes postoperative mortality, reoperation, prolonged hospitalization and hospital readmission in the study population. The PAF represents the percentage reduction in the frequency of a given outcome (e.g. mortality) that would occur in a theoretical scenario where a specific complication (e.g. anastomotic leakage) was able to be completely prevented in our study population.

Results

Some 4096 patients were analysed. Pulmonary complications and anastomotic leakage had the greatest overall impact on postoperative mortality (risk-adjusted PAF: 44.1 and 30.4 per cent, respectively), prolonged hospitalization (risk-adjusted PAF: 31.4 and 30.9 per cent, respectively) and hospital readmission (risk-adjusted PAF: 7.3 and 14.7 per cent, respectively). Anastomotic leakage had the largest impact on reoperation (risk-adjusted PAF: 47.1 per cent). In contrast, the impact of other complications on these outcomes was relatively small.

Conclusion

Reducing the incidence of pulmonary complications and anastomotic leakage may have the greatest clinical impact on outcomes after oesophagectomy.

INTRODUCTION

Oesophagectomy has an important role in the treatment of oesophageal cancer, but is accompanied by a high operative risk[1]. Reported overall frequency rates of complications after oesophagectomy range from 40 to 60 per cent, with pulmonary and anastomotic complications being the most common complications[2–5]. These postoperative complications have a significant effect on morbidity, length of hospital stay, mortality and health care costs[6–9]. Although advances in surgical techniques and perioperative care have reduced the frequency of complications over the years, postoperative morbidity remains high[10,11]. Therefore, further quality improvement efforts in oesophageal surgery are needed.

In order to develop and prioritize quality improvement initiatives, complications that have the greatest overall impact on outcomes after oesophagectomy have to be identified. Several studies have been published describing the incidence of specific complications after oesophageal surgery and the associations between these complications and subsequent outcomes[6,7,12,13]. However, simple data on the frequency of a complication is not sufficient to establish the overall impact on a patient population.

The population-attributable fraction (PAF) is a parameter that has traditionally been used in epidemiologic literature to determine the burden of a given disease (e.g. cancer) that is caused by a specific risk factor (e.g. smoking)[14–16]. This parameter is also an attractive measure to assess the overall impact of specific postoperative complications on a given outcome because it incorporates knowledge of the frequency of a complication and also the relative risk of a given outcome in the presence of that complication[16]. For example, in the context of the present study the PAF represents the percentage reduction in the frequency of a given outcome (e.g. mortality) that would occur in a theoretical scenario where a specific complication (e.g. anastomotic leakage) could be abandoned in the study population.

Recent studies have used this methodology to analyse the effect of complications after colon and vascular surgery, and reported new insights in their field of surgery[17–20]. For this reason the surgical community recently encouraged researchers to extend this methodology to other surgical populations, as this will facilitate the development of more targeted and effective surgical quality improvement programs[17,18]. Accordingly, the aim of this study was to use the PAF to identify the most clinically relevant complications following oesophagectomy for cancer.

METHODS

Patient data were obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA). The DUCA, founded in 2011, is a nationwide registration of all patients undergoing surgery with curative intent for oesophageal or gastric cancer in the Netherlands[21,22]. The DUCA collects preoperative, intraoperative as well as postoperative data to provide surgical teams with periodical feedback on process and outcome measures. It is thought that the DUCA may improve the quality of cancer care by stimulating quality improvements. Participation is mandatory for all Dutch hospitals performing oesophagectomies and gastrectomies. Data are registered during hospitalization until 30 days after initial discharge in the online registry program. Detailed descriptions of definitions are provided to ensure uniform data registration. An independent monitoring team audits the data to evaluate completeness and concordance. This study was approved by the scientific committee of the DUCA and according to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands.

Study population and treatment

All consecutive patients that underwent an elective resection for primary oesophageal cancer (cT1N+ or cT2-4aN_{any}) between January 2011 and December 2016 were identified from the DUCA. Surgical treatment consisted of an open (both abdomen and chest), hybrid (abdomen minimally invasive and open chest), or totally minimally invasive transthoracic or transhiatal oesophagectomy followed by gastric-tube reconstruction with a cervical or intrathoracic anastomosis. Patients received neoadjuvant treatment according to national guidelines.

Patient and treatment-related characteristics, complications and study outcomes

Patient and treatment-related characteristics included: gender, age, body mass index (BMI), American Society of Anaesthesiologists (ASA) score, comorbidity, previous abdominal or thoracic surgery, steroid use, surgical approach, conversion during surgery, location of anastomosis, tumour location, histology of the tumour, cTNM stage and type of neoadjuvant therapy (Table 1).

The most common postoperative complications that occurred during hospital admission or readmission (within 30 days) were retrieved from the DUCA. Selected complications included pulmonary complications (clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema and/or acute respiratory distress syndrome [ARDS]), clinically or radiologically proven anastomotic leakage, cardiac complications (supra- and ventricular arrhythmia, myocardial infarction and/or heart failure), chyle leakage, acute delirium,

recurrent nerve paresis, wound infection, thromboembolic events (pulmonary embolism and/or deep venous thrombosis) and postoperative bleeding (Table 2).

The study outcomes included postoperative mortality during initial hospital admission or within 30 days after surgery, reoperation (defined as a postoperative surgical procedure under general anaesthesia), prolonged hospitalization, and hospital readmission within 30 days after initial discharge. Prolonged hospitalization was defined as a length of hospital stay above or equal to the 75th percentile for each surgical approach (≥24 days for transthoracic open, ≥21 days for transthoracic minimally invasive, ≥23 days for transthoracic hybrid, ≥15 days for transhiatal open, and ≥20 days for transhiatal minimally invasive) in order to account for differences between surgical procedures (Table 2).

Statistical analysis

Patient and treatment-related characteristics were described as count with percentages, mean with standard deviation (SD) or median with interquartile range (IQR). Missing data were considered at random and handled using imputation with the iterative Markov chain Monte Carlo method (5 iterations)[23]. The frequency of missing values per variable before imputation are presented in Table 1 and 2. Statistical analysis was undertaken using SPSS version 24.0 (IBM Corp., Armonk, NY) and R language environment (version 3.3.1, http://www.R-project.org, 'geeglm', 'sandwich', 'mice', 'AF' packages). A *p*-value of <0.05 was considered statistically significant.

The frequency of complications and of the 4 outcome measures were calculated. Prior to analysis, a directed acyclic graph (DAG) was created to visualize the potential causal pathways from postoperative complications to the study outcomes, and to identify potential sources of confounding (www.dagitty.net/mEpwOF4)[24]. The pathways displayed in the graph were based on associations identified in previous literature[25–29] or, if the former was lacking, on plausible assumptions[30]. The DAGitty web-based software interface (version 2.3) was used to select a sufficient set of variables for adjustment to minimize bias[31]. The selected confounders included gender (binary), age (continuous), BMI (continuous), ASA (I, II, III and IV) , each of the comorbidities presented in Table 1 (binary), previous abdominal or thoracic surgery (binary), steroid usage (binary), conversion during surgery (binary), location of anastomosis (binary), surgical approach (open transthoracic, minimally invasive transthoracic, hybrid, open transhiatal, minimally invasive transhiatal), neoadjuvant therapy (none, neoadjuvant chemoradiotherapy, chemotherapy). The adjusted relative risk (aRR) for each complication-outcome pair was calculated using multivariable Poisson regression models with log link and

robust error variance, while conditioning for the selected confounders (with 95% confidence interval [95%CI]).

Accordingly, for each complication-outcome pair with a significant association in the previous analyses, the risk-adjusted PAF was calculated while adjusting for the previously mentioned confounders and for the presence of other complications. The PAF calculations were performed with the AF package in R software which allows for confounder-adjusted estimation of PAFs for cohort studies[32].

The risk-adjusted PAF was used to assess the overall impact that each of the postoperative complications had on each of the study outcomes in our study population. In this study the risk-adjusted PAF represents the percentage reduction in the frequency of a given outcome (i.e. postoperative mortality, prolonged hospitalization, reoperation and hospital readmission) that would occur in a theoretical scenario where a specific complication could be completely prevented in the present study population.

RESULTS

Patient and treatment characteristics

A total of 4096 patients with oesophageal cancer that underwent transthoracic or transhiatal oesophagectomy with gastric-tube reconstruction were eligible for analysis. Of the 4096 patients, 3168 (77.3 per cent) patients were male and the mean age was 65 years (s.d. 8.8). Patient and treatment characteristics are shown in *Table 1.*

Complications and study outcomes

Postoperative complications and outcome data are shown in *Table 2*. The most common postoperative complications were pulmonary complications that occurred in 1257 of 4096 (30.7 per cent) patients, anastomotic leakage in 807 of 4096 (19.7 per cent) and cardiac complications in 555 of 4096 (13.5 per cent). Postoperative mortality occurred in 142 of 4096 of the patients (3.5 per cent), prolonged hospitalization in 1057 of 4096 (25.8 per cent), reoperation in 576 of 4096 (14.1 per cent) and hospital readmission in 546 of 4096 patients(13.3 per cent). The median length of hospitalization was 12 days (IQR 9-20).

The risk-adjusted associations between postoperative complications and outcomes are shown in *Table 3.* Pulmonary complications and anastomotic leakage were associated with the greatest relative risk of postoperative mortality (aRR: 3.98 [95 per cent c.i. 2.79 to 5.77] and 3.64 [2.59 to 5.10], respectively). All postoperative complications were significantly associated

with prolonged hospitalization, with pulmonary complications (aRR: 3.29 [2.90 to 3.75]) and with anastomotic leakage (aRR: 3.92 [3.46 to 4.43]) having the strongest association. Apart from recurrent nerve paresis, all of the postoperative complications were statistically significant associated with reoperation. Anastomotic leakage and post-operative bleeding were associated with the greatest relative risk of reoperation (aRR: 6.11 [5.15 to 7.25] and 5.79 [4.03 to 8.07], respectively). Anastomotic leakage and wound infection were associated with the greatest relative risk of hospital readmission (aRR: 1.93 [1.61 to 2.31] and 1.79 [1.27 to 2.46], respectively).

The risk-adjusted PAF for each complication-outcome pair is shown in *Table 4* and summarized in *Figure 1.* Based on the risk-adjusted PAFs, pulmonary complications and anastomotic leakage had the greatest overall impact on postoperative mortality. Complete elimination of these complications in the present study population would result in an anticipated reduction of 44.1 per cent (95 per cent c.i. 30.9 to 57.2) and 30.4 per cent (19.2 to 41.7) in postoperative mortality, respectively. Anastomotic leakage was the complication with the greatest overall impact on reoperation (PAF: 47.1 per cent [42.2 to 51.9]), prolonged hospitalization (PAF: 31.4 per cent [28.2 to 34.6]), and hospital readmission (PAF: 14.7 per cent [9.9 to 19.5]). Pulmonary complications also had a large impact on reoperation (PAF: 17.7 per cent [11.8 to 23.6]), prolonged hospitalization (PAF: 31.4 per cent [28.2 to 34.6]), and hospital readmission (PAF: 7.3 per cent [1.2 to 13.4]). In contrast, the impact of the other postoperative complications on the selected study outcomes was relatively small.

TABLE 1. Patient and treatment-related characteristics of 4096 patients that underwent oesophagectomy for cancer.

Characteristic	No. (%)	Initial missing values§
Gender (% male)	3168 (77.3)	1
Age (years)*	65±8.8	9
BMI (kg/m^2)*	26±4.4	38
ASA score (%):		24
I	710 (17.3)	
II	2490 (60.8)	
III	881 (21.5)	
IV	15 (0.4)	
Comorbidity (%):		
Asthma / COPD	587 (14.3)	0
Coronary artery disease†	257 (6.3)	0
History of myocardial infarction	260 (6.3)	0
History of arrhythmia	329 (8.0)	0
Hypertension	1345 (32.8)	0
Peripheral vascular disease	157 (3.8)	0
Diabetes mellitus	619 (15.1)	0
History of CVA	122 (3.0)	0
History of thromboembolic events	168 (4.1)	0
Endocrine disorder	162 (4.0)	0
Previous abdominal or thoracic surgery	1238 (30.2)	0
Steroid use	104 (2.5)	34
Surgical approach (%):		0
Transthoracic		
Open	636 (15.5)	
Minimally invasive	1981 (48.4)	
Hybrid	130 (3.2)	
Transhiatal		
Open	962 (23.5)	
Minimally invasive	387 (9.4)	
Conversion during surgery	104 (2.5)	0
Location of anastomosis (%):		63
Cervical	2744 (67.0)	
Intrathoracic	1352 (33.0)	
Tumor location (%):‡		24
Proximal oesophagus	42 (1.0)	
Middle oesophagus	496 (12.1)	
Distal oesophagus	2603 (63.5)	
Gastro-oesophageal junction	955 (23.3)	
Histology tumour (%):		29
Adenocarcinoma	3201 (78.1)	
Squamous cell carcinoma	811 (19.8)	
Other	84 (2.1)	

TABLE 1 (continued). Patient and treatment-related characteristics of 4096 patients that underwent oesophagectomy for cancer.

Characteristic	No. (%)	Initial missing values§
cT category (%):		175
T1	225 (5.5)	
T2	794 (19.4)	
T3	2947 (71.9)	
T4	109 (2.7)	
cN category (%):		172
N0	1486 (36.3)	
N1	1729 (42.2)	
N2	761 (18.6)	
N3	120 (2.9)	
Neoadjuvant therapy (%):		21
Chemoradiotherapy	3478 (84.9)	
Chemotherapy	282 (6.9)	
No therapy	336 (8.2)	

Values in parentheses are percentages unless indicated otherwise. Data shown in Table represent the data set after imputation. *Data are depicted as mean ± standard deviation. BMI: body mass index (calculated as weight in kilograms divided by height in meters squared). ASA: American Society of Anaesthesiologists. COPD: chronic obstructive pulmonary disease. †Patients with a history of angina pectoris, percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG). CVA: cerebrovascular accident. ‡Proximal indicates 15-23 cm from teeth; middle indicates 24-32 cm from teeth; distal indicates 32-40 cm from teeth. §Number of missing values for each variable before imputation.

TABLE 2. Postoperative complications and clinical outcomes after oesophagectomy in 4096 patients.

Outcome	No. (%)	Initial missing values¶¶
Postoperative complications		
Pulmonary *	1257 (30.7)	0
Anastomotic leakage†	807 (19.7)	0
Cardiac ‡	555 (13.5)	0
Chyle leakage	313 (7.6)	0
Acute delirium	212 (5.2)	0
Recurrent nerve paresis§	201 (4.9)	0
Wound infection	180 (4.4)	0
Thromboembolic ¶	94 (2.3)	0
Post-operative bleeding	46 (1.1)	0
Clinical outcomes		
Postoperative mortality#	142 (3.5)	0
Duration of hospital stay (days)**	12 (9.0-20.0)	46
Prolonged hospitalization††	1057 (25.8)	46
Reoperation‡‡	576 (14.1)	0
Hospital readmission§§	546 (13.3)	0

Values in parentheses are percentages unless indicated otherwise. Data shown in Table represent the data set after imputation. *Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). †Any clinically or radiologically proven anastomotic leakage. ‡Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. §Any vocal cord dysfunction after resection. ¶Pulmonary embolism and/or deep venous thrombosis. #Death during initial hospital admission or within 30 days after surgery. **Data are depicted as median (IQR). ††Length of hospital stay $\geq 75^{th}$ percentile (for each surgical approach). ‡‡ Postoperative surgical procedure under general anaesthesia. §§Readmission to hospital within 30 days after initial discharge. ¶¶Number of missing values for each variable before imputation.

TABLE 3. Risk-adjusted associations between postoperative complications and outcomes after oesophagectomy for cancer.

	Outcome: postoperative mortality#			**Outcome: prolonged hospitalization††**		
Postoperative complication	No. died/survived (% died)	aRR (95%CI)	*p*-value	No. with/without prolonged stay (% prolonged)	aRR (95%CI)	*p*-value
Pulmonary *	96/1161 (7.6)	3.98 (2.79-5.77)	<0.001	642/615 (51.1)	3.29 (2.90-3.75)	<0.001
Anastomotic leakage†	71/736 (8.8)	3.64 (2.59-5.10)	<0.001	527/280 (65.3)	3.92 (3.46-4.43)	<0.001
Cardiac ‡	42/513 (7.6)	2.09 (1.43-3.01)	<0.001	248/307 (44.7)	1.78 (1.54-2.06)	<0.001
Chyle leakage	17/296 (5.4)	1.36 (0.78-2.24)	0.229	136/177 (43.5)	1.79 (1.48-2.15)	<0.001
Acute delirium	14/218 (6.0)	1.33(0.73-2.26)	0.30	127/105 (54.7)	2.11 (1.65-2.42)	<0.001
Recurrent nerve paresis§	3/198 (1.5)	0.37 (0.12-1.16)	0.087	69/132 (34.3)	1.28 (1.06-1.57)	0.013
Wound infection	5/175 (2.8)	0.78 (0.28-1.72)	0.571	78/102 (43.3)	1.63 (1.28-2.05)	<0.001
Thromboembolic ¶	11/83 (11.7)	3.24 (1.63-5.81)	<0.001	59/35 (62.8)	2.39 (1.82-3.9)	<0.001
Post-operative bleeding	7/39 (15.2)	3.37 (1.37-7.00)	0.006	32/14 (69.6)	2.47 (1.69-3.47)	<0.001
	Outcome: reoperation‡‡			**Outcome: hospital readmission§§**		
Postoperative complication	No. with/without reoperation (% reoperation)	aRR (95%CI)	*p*-value	No. with/without readmission (% readmission)	aRR (95%CI)	*p*-value
Pulmonary *	314/943 (25.0)	2.45 (2.07-2.90)	<0.001	211/1046 (16.8)	1.40 (1.17-1.67)	<0.001
Anastomotic leakage†	350/457 (43.4)	6.11 (5.15-7.25)	<0.001	179/628 (22.2)	1.93 (1.61-2.32)	<0.001
Cardiac ‡	128/427 (23.1)	1.66 (1.35-2.02)	<0.001	89/466 (16.0)	1.21 (0.96-1.52)	0.069
Chyle leakage	82/231 (26.2)	1.78 (1.39-2.26)	<0.001	56/257 (21.8)	1.29 (0.99-1.69)	0.051
Acute delirium	62/170 (26.7)	1.86 (1.41-2.41)	<0.001	33/199 (14.2)	1.04 (0.71-1.46)	0.812
Recurrent nerve paresis§	35/166 (17.4)	1.18 (0.82-1.64)	0.299	25/176 (12.4)	0.94 (0.61-1.38)	0.76
Wound infection	48/132 (26.7)	2.02 (1.48-2.69)	<0.001	39/141 (21.7)	1.79 (1.27-2.46)	<0.001
Thromboembolic ¶	28/66 (29.8)	2.03 (1.35-2.92)	<0.001	17/77 (18.1)	1.41 (0.84-2.22)	0.123
Post-operative bleeding	37/9 (80.4)	5.79 (4.03-8.07)	<0.001	10/36 (21.7)	1.69 (0.98-2.90)	0.058

*Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). †Any clinically or radiologically proven anastomotic leakage. ‡Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. §Any vocal cord dysfunction after resection. ¶Pulmonary embolism and/or deep venous thrombosis. #Death during initial hospital admission or within 30 days after surgery. aRR: Adjusted relative risk. †† ≥75th percentile of length of hospital stay. ‡‡ Postoperative surgical procedure under general anaesthesia. ¶¶Readmission to hospital within 30 days after initial discharge.

TABLE 4. Risk-adjusted population attributable fractions (PAF) for each pair of postoperative complication-outcome *.

Postoperative complication	%PAF (95%CI) Postoperative mortality**	*p*-value	Prolonged hospitalization††	*p*-value
Pulmonary †	44.1 (30.9-57.2)	<0.001	31.4 (28.2-34.6)	<0.001
Anastomotic leakage‡	30.4 (19.2-41.7)	<0.001	30.9 (27.1-34.8)	<0.001
Cardiac §	8.6 (-0.7-17.9)	0.070	4.0 (1.9-5.9)	<0.001
Chyle leakage	-	-	5.2 (3.6-6.8)	<0.001
Acute delirium	-	-	2.3 (0.9-3.7)	<0.001
Recurrent nerve paresis¶	-	-	0.4 (-0.7-1.5)	0.496
Wound infection	-	-	1.7 (0.6-2.7)	0.002
Thromboembolic #	3.7 (-0.4-8.0)	0.077	1.6 (0.9-2.4)	<0.001
Post-operative bleeding	2.8 (0.7-4.8)	0.008	1.2 (0.5-1.8)	<0.001
Postoperative complication	**%PAF (95%CI) Reoperation‡‡**	***p*-value**	**Hospital readmission§§**	***p*-value**
Pulmonary #	17.7 (11.8-23.6)	<0.001	7.3 (1.2-13.4)	0.017
Anastomotic leakage**	47.1 (42.2-51.9)	<0.001	14.7 (9.9-19.5)	<0.001
Cardiac ††	3.1 (-0.1-6.3)	0.054	-	-
Chyle leakage	5.7 (3.2-8.2)	<0.001	-	-
Acute delirium	1.7 (-0.4-3.9)	0.114	-	-
Recurrent nerve paresis‡‡	-	-	-	-
Wound infection	2.8 (0.9-4.6)	0.003	2.8 (0.7-4.8)	0.009
Thromboembolic §§	0.9 (-0.6-2.4)	0.260	-	-
Post-operative bleeding	4.6 (2.9-6.2)	<0.001	-	-

*PAF represents the percentage reduction in the frequency of a given outcome that would occur in a theoretical scenario where a specific complication was able to be completely prevented in our study population, after adjustment for patient and treatment-related factors. †Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). ‡Any clinically or radiologically proven anastomotic leakage. §Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. ¶Any vocal cord dysfunction after resection. #Pulmonary embolism and/or deep venous thrombosis. **Death during initial hospital admission or within 30 days after surgery. †† $\geq 75^{th}$ percentile of length of hospital stay. ‡‡ Postoperative surgical procedure under general anaesthesia. §§Readmission to hospital within 30 days after initial discharge.

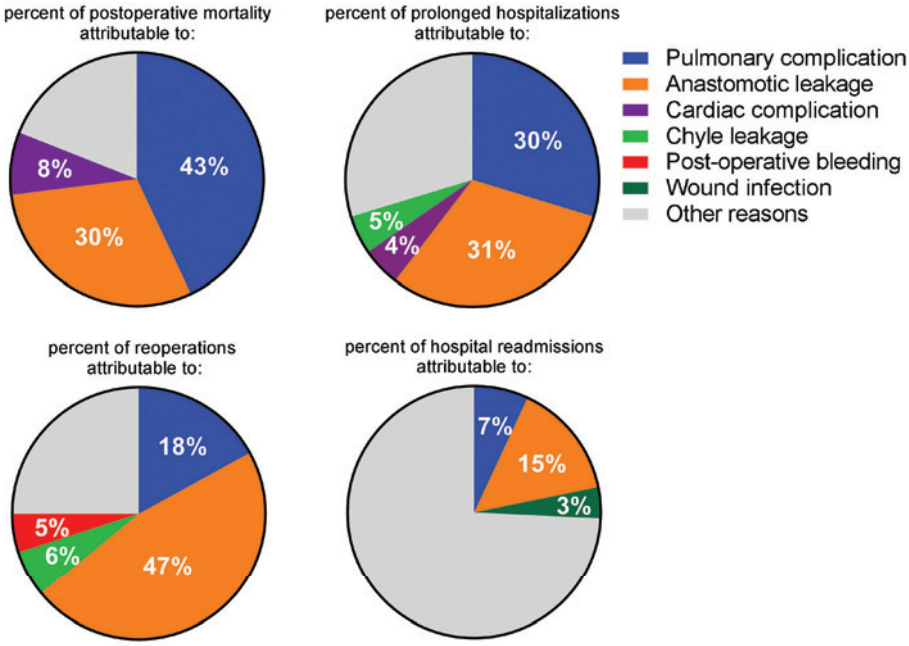

Figure 1. Risk-adjusted population attributable fractions (PAF) of the most contributing complications for each outcome.

DISCUSSION

In this nationwide cohort study the most clinically relevant complications following oesophagectomy in patients with newly diagnosed oesophageal cancer were identified by using the PAF as measure of overall impact. Pulmonary complications and anastomotic leakage had the greatest overall impact on postoperative mortality, prolonged hospitalization, reoperations and hospital readmissions.

In this study the PAF was used to quantify the proportion of an outcome in the total population that can be attributed to a specific postoperative complication[14–16]. The advantage of using this parameter is that it combines both the frequency of a complication and the relative risk of a given outcome in the presence of that complication. For example, a particularly severe complication may have a small population-level impact if it occurs rarely or vice versa. Accordingly, assessing the impact of postoperative complications by using the PAF may guide policymakers prioritizing initiatives that can reduce the clinical and economic burden of specific complications. A recent study used this methodology to quantify the impact of specific

postoperative complications on outcomes after elective colon surgery[17]. The authors concluded that their findings provided strong evidence that existing quality improvement programs were not targeting the complications that are the most relevant in colorectal surgery. Hence, this underlines the importance of gaining insight into nationwide outcomes after (oesophageal) surgery by using the PAF as parameter. Not only to stress the negative impact of postoperative complications but also to identify opportunities for improvement.

Although anastomotic leakage had a lower incidence than pulmonary complications, it had the largest clinical impact on 3 of the 4 study outcomes in the present study. If one could completely eliminate anastomotic leakage, the incidence of prolonged hospitalization, reoperation and hospital readmission would decrease by 31, 47 and 15 per cent, respectively. Pulmonary complications also had a large impact on these outcomes, and had the largest contribution to postoperative mortality (risk-adjusted PAF: 43 per cent). Interestingly, in our relative risk analysis postoperative bleeding and thromboembolic complications were both highly associated with postoperative mortality, reoperation and prolonged hospital stay. However, the PAF indicated that their impact on the total population was relatively small. Thus, even if it would be possible to reduce the incidence of postoperative bleeding and thromboembolic complications, the estimated effect of these efforts on clinical outcomes in our population would be limited. In general, findings of the present study suggest that postoperative pulmonary complications and anastomotic leakage should receive priority as targets of complication-related quality improvement initiatives in patients undergoing oesophageal resection for cancer. However, in case new initiatives are considered, it is necessary to determine which outcomes deserve the greatest attention since the impact of a specific postoperative complication depends on the outcome under investigation.

In previous literature the relevance of pulmonary complications and anastomotic leakage after oesophagectomy for cancer has been acknowledged[2–5,8,9]. Several strategies have been shown to protect against pulmonary complications and anastomotic leakage[33,34]. For anastomotic leakage this includes a precise suturing techniques with the prevention of tension and the avoidance of reduction of perfusion of the conduit, reinforcement of the anastomosis with omentoplasty, and delay of oral intake after oesophagectomy[35–37]. Pulmonary complications can be prevented by stopping smoking prior to surgery, perioperative pulmonary rehabilitation, minimally invasive surgery and effective pain mangement[34,35,38,39,40]. Furthermore, it has been shown that in high-volume centres complication rates after oesophagectomy are lower and that the use of enhanced recovery after surgery (ERAS) protocols can reduce length of hospital stay[22,36-38].

Despite the previous efforts to reduce anastomotic leakage and pulmonary complications, the proven impact of these complications justifies further initiatives to reduce the incidence and severity of these complications. Although it is unknown to what extend complications can be prevented, even a small reduction in these complications could potentially result in large hospital cost savings[9]. This effect on its own could already provide the business case for such initiatives. Furthermore, monitoring and (publically) reporting of outcomes after oesophagectomy in audits may provide healthcare providers with a very direct and tangible incentive to further explore initiatives for preventing such complications[41]. In a *market-based health care system,* hospitals that provide optimal quality of care will increase patient satisfaction and desirability with health care payers (e.g. insurance companies) resulting in enhanced referrals. On the contrary, providing low quality care will lead to poor patient outcomes, patient dissatisfaction and loss of future patient referrals[42].

In this context, it has been recognized that the anastomotic leakage rate in this cohort of patients remains high compared to other international cohort studies[43,44]. Some centres in the Netherlands have moved from a cervical to an intrathoracic anastomosis[45]. But the introduction of an intrathoracic anastomosis is first associated with a considerable learning curve[46], the leak rate may only decrease after some more years. A randomized study comparing a cervical with intrathoracic anastomosis is currently recruiting patients (ICAN trial)[47].

Methodological strengths of this study include its population-based nationwide design, the complete and validated prospective data collection and large sample size[21]. To correct for potential confounders, adjustments were made for selected patient and treatment-related characteristics. Furthermore, some patients in our study population had more than one type of complication, and therefore all 9 complications were included in our adjusted PAF analysis. Possible limitations apply to this study. First, it was not possible to specify all pulmonary and cardiac complications because the DUCA did not discriminate between pneumonia, pleural effusion and pleural empyema, or atrial fibrillation and myocardial infarction. According to literature it is most likely that pneumonia represents the majority of the pulmonary complications and atrial fibrillation the majority of cardiac complications[6,33,38]. Second, it is not always clear whether a postoperative complication (e.g. pulmonary complications) caused a given outcome (e.g. prolonged hospitalization) or conversely the complication occurred as a result of the outcome. Third, there is a possibility that the associations between postoperative complications and subsequent outcomes are influenced by unknown confounding variables. Finally, perioperative care and management of postoperative complications change overtime which also may have influenced these associations.

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Aortic calcification increases the risk of anastomotic leakage after Ivor-Lewis esophagectomy

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ABSTRACT

Objective

Anastomotic leakage is associated with increased morbidity and mortality after esophagectomy. Calcification of the arteries supplying the gastric tube has been identified as risk factor for leakage of the cervical anastomosis, but its potential contribution to the risk of intrathoracic anastomotic leakage has not been elucidated. The purpose of this study was to evaluate the relationship between calcification and the occurrence of leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy.

Methods

Consecutive patients who underwent minimally invasive esophagectomy for cancer at two institutes were analyzed. Diagnostic computed tomography images were used to detect calcification of the arteries supplying the gastric tube (e.g. aorta, celiac axis). Multivariable logistic regression analysis was used to determine the relationship between vascular calcification and anastomotic leakage.

Results

Of 167 included patients, 40 (24%) experienced anastomotic leakage. In univariable analysis, leakage was most frequently observed in patients with calcification of the aorta (major calcification; 37% leakage [16 of 43], and minor calcification; 32% [18 of 56] versus absence of calcification; 9% [6 of 70], $p<0.001$). Calcification of other studied arteries was not significantly associated with leakage. Minor and major aortic calcifications remained significantly associated with leakage in multivariable analysis (odds ratio [OR] 5.4, 95% confidence interval [CI]:1.7–16.5, and OR 7.0, 95% CI:1.9–26.4; respectively).

Conclusion

Atherosclerotic calcification of the aorta is an independent risk factor for leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy for cancer. The calcification scoring system may aid in patient selection and lead to earlier diagnosis of this potentially fatal complication.

INTRODUCTION

Surgical resection of the esophagus combined with neoadjuvant chemoradiation or perioperative chemotherapy is the cornerstone of treatment with curative intent for patients with resectable non-metastatic esophageal cancer[1-3]. Anastomotic leakage is a frequently encountered complication after esophagectomy that is associated with increased postoperative morbidity, length of hospital stay and mortality[4-7]. Furthermore, anastomotic leakage has been shown to negatively affect long-term cancer specific-survival after esophagectomy[8]. Despite advances in surgical treatment and improvement in perioperative care, incidence rates of up to 24-30% have been reported for anastomotic leakage after esophagectomy[3,9].

Identifying risk factors for anastomotic leakage after esophagectomy could aid in early recognition and subsequently limit the impact of this complication. Currently it is difficult to accurately predict anastomotic leakage based on standard patient or treatment-related characteristics only. Tissue ischemia and a compromised perfusion of the gastric tube are considered the main causes of insufficient anastomotic healing[4,10]. As an important contributor to tissue ischemia, atherosclerosis is associated with a detrimental effect on anastomotic healing[11]. In a recently published study, atherosclerotic calcification of the arteries supplying the gastric tube as determined by routine diagnostic computed tomography (CT) scans was identified as independent risk factor for anastomotic leakage of the cervical anastomosis after esophagectomy[12].

The potential contribution of atherosclerotic calcification to the risk of anastomotic leakage after esophagectomy with an intrathoracic anastomosis has not been elucidated. The shorter length of the gastric tube in case of an intrathoracic anastomosis may cause relatively less ischemia compared to a cervical anastomosis[5]. Accordingly, the aim of this study was to evaluate the relationship between atherosclerotic calcification of the arteries supplying the gastric tube (as determined by scoring calcifications on CT) and the occurrence of leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy for cancer.

METHODS

Study population

The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived. All consecutive patients who underwent an elective, minimally invasive Ivor-Lewis esophagectomy for cancer in the Catharina Hospital, Eindhoven, and the Ziekenhuisgroep Twente, Almelo, between April 2012 and March 2015 were selected from prospectively collected institutional databases. Within these databases, patients with

an available preoperative thoraco-abdominal contrast-enhanced CT scan were included. All patients underwent a total minimally invasive esophagectomy with gastric tube reconstruction using an intracorporal anastomosis. The intrathoracic anastomosis was created using a side-to-side linear stapling technique or end-to-side hand-sewn technique at the level of the carina. Patients who underwent preoperative vascular conditioning (e.g. stenting of the celiac artery) or a reconstruction other than a gastric tube were excluded from this study. Patient and treatment-related characteristics from the remaining eligible patients were extracted from the prospectively acquired databases. Parameters of interest included gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, chronic obstructive pulmonary disease (COPD), coronary artery disease and other cardiac co-morbidity, hypertension, peripheral vascular disease, diabetes mellitus, smoking status at diagnosis, neoadjuvant treatment and anastomotic technique.

Image acquisition and evaluation

Thoraco-abdominal CT images were acquired using commercially available 16- or 64-section CT scanners at our own or referring centers. All contrast-enhanced routine CT protocols were considered suitable if the field-of-view at least included the total thoracic aorta, celiac axis, right postceliac arteries (i.e. common hepatic, gastroduodenal, and right gastroepiploic arteries) and left postceliac arteries (splenic and left gastroepiploic arteries). Images were acquired with a slice thickness of 2 mm (5% of patients), 2.5 mm (12% of patients), 3.0 mm (47% of patients) or 5 mm (36.0% of patients). In case more than one CT scan was available, the first diagnostic scan conducted during the diagnostic work-up was used. In all patients an iodinated contrast bolus was administered intravenously. The CT images were acquired during either the arterial phase or the portal venous phase.

The CT images were retrospectively reviewed and scored for location and amount of calcification by one reader (L.G.). The reader was trained to use a previously described simple vascular scoring system for calcifications of the arteries of the gastric tube[12] by the authors that proposed the system using a training set of 25 randomly selected patients who were not part of the study sample. This scoring system has been shown to yield good to excellent inter- and intraobserver reproducibility[12]. The reader was blinded to patient and treatment-related characteristics and surgical outcome.

Calcification of the thoracic aorta was scored on transverse CT images from the origin of the left subclavian artery, down to the origin of the celiac axis (score 0-2). An aortic calcification score of 1 was assigned in case of nine or fewer calcified foci and three or fewer calcified

foci extending over three or more contiguous axial images. A score of 2 was assigned in case more than nine calcified foci or more than three calcified foci extending over three or more contiguous axial images were observed. Also, calcification of the celiac axis was scored (score 0-2). A score of 1 was assigned when calcifications extended over fewer than three contiguous axial images or a single calcified focus was smaller than or equal to 10 mm (long axis). In case of larger calcifications or involvement of both the proximal (aortoceliac) and distal (hepatosplenic bifurcation) parts of the celiac axis, a score of 2 was assigned. Scores of 0, 1 and 2 were considered as absence, minor or major presence of calcification, respectively. The right postceliac arteries and left postceliac arteries were scored according to the absence or presence of calcification (score 0-1). The threshold of 3 or more contiguous axial images was initially proposed for CT-scans with 5 mm slices. In case of thinner slices the grading system was adjusted accordingly. Examples of image characteristics are presented in Figure 1.

Statistical analysis

The primary outcome measure of this study was anastomotic leakage defined as either clinical signs of leakage from a thoracic drain, radiological signs of leakage including contrast leakage or fluid and air levels surrounding the anastomosis, or signs of anastomotic dehiscence during endoscopy or re-operation. In case anastomotic leakage was clinically suspected, a CT scan or endoscopy was performed; no routine diagnostic tests were performed[13].

The association of patient and treatment-related characteristics and calcification scores with anastomotic leakage was studied univariably. Categorical parameters were compared using the Chi-square test or Fisher's exact test in case of small cell count. The Student's T-test and Mann-Whitney U test were used to compare groups with and without anastomotic leakage for parametric and non-parametric continuous parameters, respectively. Subsequently, variables with $p \leq 0.25$ in univariable analysis were entered in a multivariable logistic regression model to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage. Odds ratios (ORs) with 95% confidence intervals (CIs) were provided. Statistical analysis was performed using SPSS 20.0 (IBM Corp. Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

In the study period, a total of 170 patients underwent a total minimally invasive esophagectomy with gastric tube reconstruction and intrathoracic anastomosis (Ivor-Lewis). Of these patients, three were excluded because no gastric tube formation could be performed during surgery (n=1) or preoperative vascular conditioning was performed (n=2). Forty (24%) of the remaining

167 patients experienced anastomotic leakage, occurring after a median time of 5 days (range 1-14) after esophagectomy. Of these, 10 patients (25%) showed some signs of tissue ischemia or necrosis of the gastric conduit during postoperative endoscopy. Treatment of anastomotic leakage consisted of antibiotics and nil-by-mouth in 4 of 40 patients (10%), endoscopic re-intervention (stent placement or mediastinal drainage) in 18 patients (45%), and surgical re-intervention in 18 patients (45%). Baseline patient and treatment-related characteristics are presented in Table 1. None of these characteristics were significantly associated with the occurrence of anastomotic leakage in univariable analysis. However, patients with anastomotic leakage had a slightly higher age compared to patients without anastomotic leakage (mean: 66.5 versus 63.5 years, respectively; p=0.053).

The overall prevalence of calcification of the studied arteries including the thoracic aorta, celiac axis and left postceliac arteries was high (i.e. 59%, 43% and 25%, respectively). In contrast, calcification of the right postceliac arteries was found in only 5 (3%) of 167 patients. A comparison of calcification per trajectory for patients with versus without anastomotic leakage is shown in Table 2. In univariable analysis, the presence of aortic calcification was significantly associated with a higher risk of anastomotic leakage (32% leakage [18 of 56] and 37% leakage [16 of 43] in groups with minor and major calcification, respectively, versus 9% leakage [6 of 70] in the group without calcification, p<0.001). Calcification of the celiac axis was not significantly associated with anastomotic leakage (18% leakage [7 of 39] and 33% leakage [11 of 33] in groups with minor and major calcification, respectively, versus 23% leakage [22 of 95] in the group without calcification, p=0.496). Although the risk of anastomotic leakage in patients with calcification of the right and left postceliac arteries appeared higher compared to patients without these calcifications, the risk differences were not statistically significant (40% leakage [2 of 5] versus 24% leakage [38 of 162]; p=0.393, and 32% leakage [13 of 41] versus 21% [27 of 126]; p=0.180, respectively).

Age and presence of coronary artery disease along with the calcification scores of the aorta and left postceliac arteries were selected for multivariable logistic regression analysis (Table 3). Minor (score 1) and major (score 2) aortic calcification remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted OR 5.35, 95% CI: 1.73–16.55 and adjusted OR 7.01, CI: 1.96–26.44, respectively). Age, presence of cardiac comorbidity and calcification of the left post celiac arteries were not independently associated with anastomotic leakage in multivariable analysis.

TABLE 1. Patient and treatment-related characteristics in relation to anastomotic leakage

Characteristic	No anastomotic leakage n=127	Anastomotic leakage n=40	p value
Male gender	105 (82.7)	34 (85.0)	0.732
Age (years)*	63.5 ± 8.8	66.5 ± 9.2	0.053
BMI (kg/m^2)*	26.3 ± 4.4	26.8 ± 5.9	0.893
ASA score			0.548
I	9 (7.1)	4 (10.0)	
II	86 (67.7)	29 (72.5)	
III	32 (25.2)	7 (17.5)	
COPD	20 (15.7)	7 (17.5)	0.793
Coronary artery disease†	14 (11.0)	8 (20.0)	0.143
Other cardiac co-morbidity‡	12 (9.4)	4 (10.0)	0.564
Hypertension§	40 (31.5)	13 (32.5)	0.443
Peripheral vascular disease‖	9 (7.1)	2 (2.0)	0.643
Diabetes mellitus	22 (17.3)	6 (15.0)	0.732
Renal insufficiency ¶	7 (5.5)	2 (5.0)	1.000
Smoker at diagnosis	24 (18.9)	8 (20.0)	0.520
Neoadjuvant therapy			0.776
No therapy	10 (7.9)	4 (10.0)	
Chemotherapy	110 (86.6)	35 (87.5)	
Chemoradiotherapy	7 (5.5)	1 (2.5)	
Anastomotic technique			0.940
Side-to-side stapling	96 (75.6)	30 (75.0)	
End-to-side hand-sewn	31 (24.4)	10 (25.0)	

*Data are depicted as mean ± standard deviation.†Requiring percutaneous coronary intervention or coronary artery bypass graft. ‡A record of historical treatment of any cardiac disorder at a cardiology department (other than coronary artery disease).b§Requiring pharmacologic therapy. ‖Requiring vascular reconstruction, bypass surgery or percutaneous intervention to the extremities (excluding vein stripping) or documented aortic aneurysm with or without repair. ¶Based on a glomerular filtration rate of <60 mL/min/1.73 m^2.

TABLE 2. Distribution of calcification scores per trajectory and the proportion of patients with anastomotic leakage

Artery	**n** (%)	**Anastomotic leakage** (% of row)	**p value**
Thoracic aorta			<0.001
0	68 (40.7)	6 (8.8)	
1	56 (33.5)	18 (32.1)	
2	43 (25.7)	16 (37.2)	
Celiac axis			0.496
0	95 (56.9)	22 (23.2)	
1	39 (23.4)	7 (17.9)	
2	33 (19.8)	11 (33.3)	
Right postceliac arteries			0.393
0	162 (97.0)	38 (23.5)	
1	5 (3.0)	2 (40.0)	
Left postceliac arteries			0.180
0	126 (75.0)	27 (21.4)	
1	42 (25.0)	13 (31.7)	

Data represent amount of patients with percentages.

TABLE 3. Results of multivariable logistic regression analysis in assessing risk of developing anastomotic leakage

Variable		**Odds ratio**	**95% CI**	**p value**
Thoracic aorta				
	1 vs. 0	5.35	1.73 - 16.55	0.004
	2 vs. 0	7.01	1.86 - 26.44	0.004
Left postceliac arteries				
	1 vs. 0	0.92	0.38 - 2.16	0.855
Age		0.99	0.94 - 1.04	0.669
Coronary artery disease		1.55	0.56 - 4.33	0.402

OR: Odds ratio. CI: confidence interval.

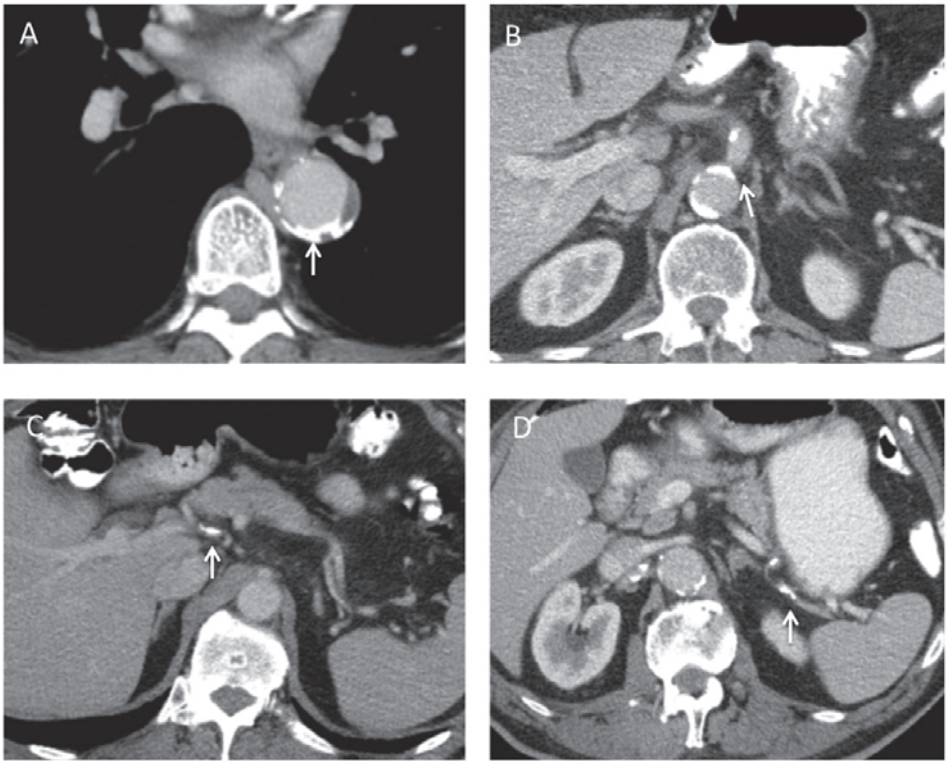

Figure 1. Examples of calcification on preoperative CT images in patients with esophageal cancer. **A:** Image shows the descending aorta with plaques and calcified foci (*arrow*), a calcification score of 2 was assigned. **B:** Image shows calcification of the celiac axis (*arrow*), a calcification score of 2 was assigned**. C:** Image shows calcification of the common hepatic artery (*arrow*), yielding a right postceliac artery calcification score of 1. **D:** Image shows calcified foci in the splenic artery (*arrow*), yielding a left postceliac artery score of 1.

DISCUSSION

Accurate risk assessment of anastomotic leakage after esophagectomy could aid in the selection of patients who may benefit from pre-operative preventative strategies and postoperative decision-making. Unfortunately, we are currently not able to accurately predict anastomotic leakage after esophagectomy using standard patient or treatment-related characteristics. This study demonstrates that the presence and severity of calcification of the thoracic aorta, as determined on routine preoperative CT images, are independently associated with the risk of leakage of the intrathoracic anastomosis after esophagectomy for cancer. The calcification scoring method deserves attention and validation as a risk factor in future prediction models to identify patients at high risk for leakage.

This study used a previously described system for grading calcification of the arteries of the gastric tube, which has been shown to yield good to excellent inter- and intra-observer reproducibility[12]. In turn, this calcification grading system was based on a validated visual grading system used to score vascular calcification on routine diagnostic CT images for the prediction of cardiovascular events[14,15]. Our observed association between aortic calcification and leakage of the intrathoracic anastomosis corresponds with the results of a previous study that identified calcification of the aorta and right postceliac arteries as independent risk factor for leakage of the cervical anastomosis after esophagectomy[12]. Similarly, another study identified calcification of the iliac arteries as risk factor for anastomotic leakage after colorectal surgery[16]. Therefore, the current study adds to the increasing body of evidence on the association between atherosclerotic calcification and leakage of gastro-intestinal anastomoses.

Tissue ischemia, potentially resulting in anastomotic leakage, is thought to be moderated by both compromised local perfusion and generalized vascular disease (indicated by aortic calcification)[11,12,17,18]. During mobilization of the stomach, the left and right gastric artery, short gastric arteries, and left gastroepiploic artery are ligated, causing the blood supply of the gastric tube to depend exclusively on the right gastroepiploic artery[19]. This procedure results in a compromised blood flow in the most cranial part of the gastric tube, which is used to create the anastomosis. Our finding that aortic calcification rather than calcification of the smaller vessels (i.e. celiac axis and postceliac arteries) significantly increased the risk of anastomotic leakage, suggests that generalized vascular disease may be more indicative for the risk of anastomotic leakage than local vascular disease of the arteries supplying the gastric tube. Vascular calcification has been associated with many typical cardiovascular risk factors that are also associated with anastomotic leakage, such as age, diabetes, peripheral vascular disease and renal dysfunction[6]. In the current study, none of these cardiovascular co-morbidities were significantly associated with anastomotic leakage. Therefore, aortic calcification may help to identify high-risk patients who have not yet been diagnosed with these typical risk factors.

Enhancement of blood flow to the gastric tube has been suggested as possible approach to improve tissue oxygenation and anastomotic healing[20,21]. Gastric ischemic preconditioning aims to preoperatively improve blood flow to the gastric tube by laparoscopic ligation or arterial embolization of the left gastric artery prior to surgery[22,23]. Furthermore, recent experimental studies reported on novel surgical revascularization procedures that could improve blood flow at the anastomotic site, for example by increasing the length of the arterial arcade by leaving the collaterals of the left gastro-epiploic artery in situ (ligating it at the splenic hilus[24], by transient bloodletting of the short gastric vein[25], or by microvascular

additional 'supercharging' anastomoses of graft vessels to recipient vessels for microvascular blood flow augmentation at the level of the gastric tube[26]. In current clinical practice there is no strong evidence to implement ischemic conditioning and surgical revascularization procedures, which may be due to the inability to adequately identify the patients who may actually benefit from this invasive intervention[27]. The aortic calcification scoring system could aid in the selection of patients who are at high risk of anastomotic leakage, to further assess the potential benefit of these preventative interventions in clinical studies. This is supported by our finding that the absence of aortic calcification seems to have a relatively high negative predictive value for anastomotic leakage, since the observed risk of anastomotic leakage in this group was only 9%.

Recognition of the increased risk (of up to 38%) for developing anastomotic leakage in patients with major calcification of the thoracic aorta may have important implications. When confronted with this finding preoperatively, the physical condition of the patients to tolerate a leakage requires special attention. Also, postoperatively these patients should be monitored intensively for indications of clinical deterioration. Furthermore, these patient may benefit from drain amylase assessment[28] and early gastric tube assessment with endoscopy in the first week after surgery before mediastinal spread or ischemia-associated sepsis become clinically manifest. Endoscopy after esophagectomy has proven to be an accurate method to diagnose anastomotic leakage and provide information on the condition of the gastric tube[29,30]. Selecting patients for endoscopy based on a predisposed risk for anastomotic leakage could prevent an unnecessary and invasive endoscopy for a substantial proportion of patients. Therefore, a routine comment on the thoracic aortic calcium burden in the radiology report of the diagnostic thoraco-abdominal CT scan in all patients evaluated for esophageal cancer could in aid pre- and postoperative decision-making.

Postoperative anastomotic leakage was relatively common in the current series, occurring in 24% of the patients. Although this appears higher than some other studies, our definition of anastomotic leakage is rather unrestrictive including any sign of clinical or radiological evidence of leakage. As such, the leakage rate in this study appears to be comparable to the leakage rates of 22% to 30% that were reported in the recent multicenter randomized controlled CROSS-trial[3].

A few limitations apply to this study. First, this study was confined to a population that underwent elective minimally invasive Ivor-Lewis esophagectomy. Outcomes might be different in populations that undergo other surgical approaches. Second, no prospective data

is yet available to prove additional clinical benefit of the proposed calcification score in terms of morbidity reduction. Third, a visual grading system may not be the most accurate method to assess atherosclerotic calcifications, and there may be more distinct methods to analyze the extensiveness of vascular disease and local perfusion. However, the visual grading system used in the current study is easy to use, can be applied on routine diagnostic CT scans, and has been shown to yield good to excellent inter- and intra-observer reproducibility[12].

In conclusion, this study demonstrated the value of assessing atherosclerotic calcification of the thoracic aorta on routine preoperative CT images to identify patients at high risk of intrathoracic anastomotic leakage after Ivor-Lewis esophagectomy. The applied calcification scoring system may aid in patient selection for interventions that optimize the condition of the anastomosis and lead to earlier diagnosis of this potentially fatal complication.

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14

Generalized cardiovascular disease on a preoperative CT scan is predictive for anastomotic leakage after esophagectomy

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ABSTRACT

Objective

Recent studies demonstrated that calcification of arteries supplying the gastric tube is associated with anastomotic leakage after esophagectomy. However, it remains unclear whether this association only derives from local flow limitations, or generalized vascular disease as well. The purpose of this study was to determine whether calcification throughout the entire cardiovascular system is associated with anastomotic leakage.

Methods

Consecutive patients who underwent an esophagectomy with gastric tube reconstruction and cervical anastomosis for esophageal cancer were analyzed. Diagnostic CT images were scored for the presence of arterial calcification on 10 locations based on a visual grading system. The association with anastomotic leakage was studied using logistic regression analysis.

Results

A total of 406 patients were included for analysis of whom 104 developed anastomotic leakage (25.6%). Presence of calcification in the coronary arteries (minor calcification: 36.5% leakage; no calcification: 18.1%, p=.001), supra-aortic arteries (minor calcification: 30.9% leakage; major calcification: 35.3%; no calcification: 16.1%, p=.007 and p<.001, respectively) and thoracic aorta (major calcification: 33.3% leakage; no calcification: 19.4%, p=.011) was associated with leakage. In multivariable analysis, minor calcification of the coronary arteries (OR 2.29, 95% CI: 1.28-4.12, p=.005) and calcification of the supra-aortic arteries (OR 2.48, 95% CI: 1.30-4.74, p=.006 for minor calcification and OR 2.72, 95% CI: 1.49-4.99, p=.001 for major calcification) remained independently associated with leakage.

Conclusions

Calcification of the coronary and supra-aortic arteries on routine CT are predictive of cervical anastomotic leakage after esophagectomy. These results suggest that generalized cardiovascular disease is a strong indicator for the risk of leakage.

INTRODUCTION

Anastomotic leakage after esophagectomy for patients with esophageal carcinoma is a frequently encountered complication (10-30%), resulting in increased postoperative morbidity and mortality[1-9]. Several studies have aimed to identify preoperative risk factors for anastomotic leakage after esophagectomy[2,10,11]. Patient-related factors associated with anastomotic leakage include obesity, heart failure, coronary artery disease, peripheral vascular disease, hypertension, steroids, diabetes, renal insufficiency and tobacco use[2]. The majority of these risk factors underline the current hypothesis that ischemia is one of the most important contributors to anastomotic leakage, since most of these factors negatively influence microvascular perfusion and thus compromise anastomotic healing[2,4].

Preoperative identification of patients with esophageal cancer at high risk of anastomotic leakage may provide opportunities to modify these risk factors or more fully optimize patients to reduce their risk of anastomotic leakage. However, predicting anastomotic leakage based only on standard patient-related risk factors remains challenging, encouraging further research into prediction strategies[11].

Radiographic findings such as atherosclerotic calcification on a computed tomography (CT) scan can be used to objectively evaluate a patients' vascular status and risk of cardiovascular events[12-14]. Recent studies demonstrated that atherosclerotic calcification of the thoracic aorta and right postceliac arteries is associated with anastomotic leakage after esophagectomy[11,15]. To date, however, it remains unclear whether the association between anastomotic leakage and calcification detected on a CT scan applies to local vascular disease (with accompanied local flow limitations) only, or to generalized vascular disease as well. Therefore, the purpose of this study was to determine whether the presence of atherosclerotic calcification throughout the entire cardiovascular system as determined on routine CT images is associated with anastomotic leakage after esophagectomy for cancer.

METHODS

This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (number 15/624); the requirement for written informed consent was waived.

Study population

All consecutive patients who underwent elective esophagectomy for cancer with gastric tube reconstruction and handsewn cervical anastomosis from October 2003 to October 2015 at the University Medical Center Utrecht were considered for inclusion. Exclusion criteria included

premature discontinuation of surgery due to the discovery of T4b or M1 disease during surgery, combined laryngeal resection, salvage surgery and insufficient quality of CT scan.

Patient and treatment-related characteristics, and surgical outcome data (e.g. anastomotic leakage), were collected from a prospectively maintained database. Anastomotic leakage was defined by either visible loss of saliva through the cervical wound, extravasation of water-soluble contrast material during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical re-intervention.

Image acquisition

CT images of the neck, thorax and (upper) abdomen were routinely conducted during diagnostic workup with multidetector row CT scanners from various vendors at our own or referring institutions. Images were acquired with a tube potential varying from 100 to 140 kV, a minimum tube current of 8-500 mAs (median 73 mAs), a maximum tube current of 33-500 mAs (median 181 mAs) and typically with a field-of-view of 500 mm. The scans were typically contrast-enhanced (90.1%). All routine preoperative CT protocols with a maximum slice thickness ≤ 7 mm were considered suitable for inclusion. Median slice thickness was 3.0 mm (range 0.9 - 7.0 mm, IQR 4.0 mm), with a slice thickness of 5.0 mm or less in 98.8% (401/406) of patients. The interval between CT scanning and primary surgery ranged from 1 to 280 days, with a median of 114 days.

Image evaluation

A detailed visual grading system was developed in order to consistently score CT images on arterial calcification at ten different locations (Table 1). The selected locations included the supra-aortic arteries (i.e. the brachiocephalic trunk, left common carotid artery and left subclavian artery), coronary arteries, aortic valve, thoracic aorta (with special attention to a possible calcified ductus arteriosus that was not scored as a calcification), abdominal aorta, celiac axis, common iliac arteries (left and right) and external iliac arteries (left and right). Scores of 0, 1 or 2 were assigned, corresponding with absence, minor presence or major presence of calcification, respectively. Examples of arterial calcification on CT images are presented in Figure 1.

Images were typically analyzed in the transverse plane with software from Sectra: PACS IDS7™ version 17.3. All CT images were scored independently by one reader (A.S.B.), trained and supervised by a radiologist with 10 years of experience in thoracic and abdominal CT evaluation (P.A.d.J.). In addition, a random sample of 30 patients without missing data was

scored twice by one reader (A.S.B.) after a 12-month interval between readings, as well as scored independently by a second reader (L.G.) to determine intra- and interobserver reproducibility and agreement, respectively. In previous studies, this type of grading calcification has been shown to yield good to excellent intra- and interobserver reproducibility and agreement[12,15,16]. The readers were blinded for patient and treatment-related factors, and outcome in terms of anastomotic leakage.

Statistical analyses

The association between patient and treatment-related characteristics and anastomotic leakage was studied univariably. Depending on the cell count, the χ^2 or Fisher's exact test was used for categorical variables. The independent samples t-test or Mann-Whitney U test were used for normally or skewed distributed continuous variables, respectively.

The association between calcification scores and anastomotic leakage was studied per location in an univariable and multivariable logistic regression model. Variables to be entered into the multivariable logistic regression model along with the calcification score were based on clinical reasoning and literature review to be able to assess whether the calcification score was independently and significantly associated with the occurrence of anastomotic leakage (17,18). Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and Wald test statistic p-values were calculated. Surgery-related factors were excluded from this model because this parameter would not be useful in preoperative risk assessment[19].

Some CT scans did not include all regions of interest, so not all sites could be assessed for the presence of calcification (1.2% [5/406], 6.7% [27/406] and 9.1% [37/406] of the CT scans for the abdominal aorta, common iliac arteries and the external iliac arteries, respectively). These missing data were considered missing at random (MAR). Multiple imputation of these missing sites was applied to replace these missing values for logistic regression analysis, using 20 imputed datasets[20,21].

Reproducibility of the calcification scoring system within and between observers was assessed with reliability and agreement analyses. Overall proportions of agreement were calculated to determine the intra- and interobserver agreement of the calcification scoring model. Intra- and interobserver reliability for grading the calcification scores of all anatomical locations was assessed by Cohen's linearly weighted kappa (κ)[22]. The weighted κ statistic can be interpreted as follows: κ of 0.81 to 1.00 indicates excellent reliability; κ of 0.61 to 0.80, good reliability; κ

of 0.41 to 0.60, moderate reliability; κ of 0.21 to 0.40, fair reliability; and κ of less than 0.20, poor reliability[23].

Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). An online statistical tool was used to analyze reliability and agreement of the calcification scoring system (http://vassarstats.net/kappa.html). Probability values <.05 were considered to be statistically significant.

TABLE 1. Definitions used to visually grade arterial calcification on preoperative CT images

Anatomical location	**Calcification scores**		
	0	1	2
Coronary arteries	absent	multiple foci *or* 1 calcification extending over ≥2 slices	calcified arteries covering a large segment of a coronary branch
Supra-aortic arteries	absent	calcification in 1 supra-aortic artery	calcification in >1 supra-aortic artery
Aortic valve	absent	1 small calcification on 1 leaflet	> 1 small calcification on 1 leaflet
Thoracic aorta *(heart – celiac axis)*	absent	≤9 foci *or* ≤3 calcification extending over ≥3 slices	>9 foci *or* >3 calcification extending over ≥3 slices
Celiac axis	absent	single focus with MCSD ≤10 mm *or* extending over <3 slices	MCSD >10 mm *or* extending over ≥3 slices *or* involving proximal (aortoceliac) and distal (hepatosplenic) parts
Abdominal aorta *(celiac axis – bifurcation)*	absent	≤9 foci *or* ≤3 calcification extending over ≥3 slices	>9 foci *or* >3 calcification extending over ≥3 slices
Common iliac arteries	absent	≤5 foci *or* 1 calcification extending over ≥3 slices	>5 foci *or* >1 calcification extending over ≥3 slices
External iliac arteries	absent	≤5 foci *or* 1 calcification extending over ≥3 slices	>5 foci *or* >1 calcification extending over ≥3 slices

MCSD: maximum cross-sectional diameter.

RESULTS

A total of 497 patients underwent esophagectomy during the study period, of which 91 patients were excluded based because of benign disease (n = 18), non-elective surgery (n = 7), reconstruction other than gastric tube (n = 7), intrathoracic anastomosis (n = 5) premature discontinuation of surgery due to the discovery of T4b or M1 disease during surgery (n = 10), combined laryngeal resection (n = 8), salvage surgery (n = 1) and insufficient quality of CT

scan (n = 34) (Figure 2). One patient experienced a major acute myocardial infarction within 3 days after esophagectomy and was excluded from further analysis.

The 406 patients that were included for analysis had a mean age of 64 years, and 73.9% (n = 300) were male. In the majority of patients treatment consisted of neoadjuvant therapy (chemotherapy or concurrent chemoradiotherapy) followed by thoracolaparoscopic esophagectomy.

A total of 104 patients (25.6%) experienced anastomotic leakage after a median of 7 days (range, 1 to 26 days) postoperatively. Patient and treatment-related characteristics and their univariable association with anastomotic leakage are presented in Table 2. Of these variables, COPD (p=.005) and a transhiatal surgical approach (p=.024) were significantly associated with anastomotic leakage. Furthermore, patients with anastomotic leakage appeared slightly older (mean 65.5 versus 63.7 years, p=.082*)* and more frequently had a history of diabetes mellitus (19.2% versus 12.3%, p=.077).

Distribution of arterial calcification among patients with and without anastomotic leakage is shown in Table 3. For all studied vascular locations, calcifications were more frequently observed in the anastomotic leakage group compared to the group without anastomotic leakage. Only 6% (23/406) of patients did not have arterial calcifications. The absolute difference in the incidence of anastomotic leakage among patients that did not have calcifications at any location was 9% (17% (4/23) in patients without any calcifications versus 26% (100/383) in patients with calcifications).

Presence of calcification in the coronary arteries (minor calcification: 36.5% leakage [42/115], versus absence of calcification: 18.1% leakage [31/171], p=.001), supra-aortic arteries (minor calcification: 30.9% leakage [25/81], major calcification: 35.3% leakage [49/139], versus absence of calcification: 16.1% leakage [30/186], p=.007 and p<0.001, respectively), and thoracic aorta (major calcification: 33.3% leakage [40/120], versus absence of calcification: 19.4% leakage [28/144], p=.011), was significantly associated with an increased risk of anastomotic leakage in univariable logistic regression analysis. Although the prevalence of anastomotic leakage in patients with calcifications of the aortic valve, celiac axis, abdominal aorta, common and external iliac arteries appeared higher than in patients without calcification, these odds ratios were not statistically significant.

The calcification scores of the coronary arteries, supra-aortic arteries, thoracic aorta, abdominal aorta, celiac axis and external iliac arteries were entered per location into a multivariable logistic regression model, along with age, BMI, history of cardiovascular disease, COPD, diabetes mellitus and smoking (Table 3). Calcification of supra-aortic arteries remained significantly and independently associated with anastomotic leakage (OR 2.48, 95% CI: 1.30-4.74, *p*=.006 for minor calcification and OR 2.72, 95% CI: 1.49 – 4.99, *p*=.001 for major calcification), as well as minor calcification of the coronary arteries (OR 2.29, 95% CI: 1.28-4.12, *p*=.005). As an illustration: the presence of minor calcification of supra-aortic arteries increased the odds of developing anastomotic leakage with 148% compared to patients without calcification of the supra-aortic arteries.

Reproducibility of the calcification scoring system

Reproducibility between and within observers was assessed in 30 randomly selected patients that appeared to be representative of the whole study group. The randomly selected patients had a mean age of 62 years ± 11 (standard deviation) and 86% (26/30) were male. Anastomotic leakage occurred in 16.6% (5/30).

The proportion of agreement for the calcification scores was high, ranging from 73.3% to 96.7% within one observer, and from 86.7% to 96.7% between observers for the different anatomical locations (Table 4). Furthermore, the calcification score categories showed excellent intra- and interobserver reliability (κ) for all anatomical locations, ranging from 0.63 to 0.96 and from 0.85 to 0.94, respectively (Table 4).

TABLE 2. Baseline patient and treatment-related characteristics and their association with anastomotic leakage in univariable analysis

Characteristic	**Anastomotic leakage** n = 104 (25.6%)	**No anastomotic leakage** n = 302 (74.4%)	p-value
Patient-related			
Age at diagnosis (years)	65.5 ± 8.8	63.7 ± 9.1	.082
Sex (male)	82 (78.8)	218 (72.2)	.182
BMI (kg/m^2)	25.8 ± 4.3	25.5 ± 4.3	.538
ASA score			.156
1	23 (22.1)	66 (21.9)	
2	55 (52.9)	193 (63.9)	
3	26 (25.0)	42 (13.9)	
4	0 (0.0)	1 (0.3)	
Comorbidities			
COPD	24 (23.1)	37 (12.3)	.008*
Diabetes mellitus	20 (19.2)	37 (12.3)	.077
Cardiovascular[a]	46 (44.2)	110 (36.4)	.158
Smoking status			.653
Current	22 (21.2)	73 (24.2)	
Former	44 (42.3)	113 (37.4)	
Never	38 (36.5)	116 (38.4)	
Tumor histology			.742
Adenocarcinoma	82 (78.8)	227 (75.2)	
Squamous cell carcinoma	21 (20.2)	71 (23.5)	
Other[b]	1 (1.0)	4 (1.3)	
Treatment-related			
Neoadjuvant treatment			.368
None	38 (36.5)	93 (30.8)	
Chemotherapy	26 (25.0)	96 (31.8)	
Chemoradiotherapy	40 (38.5)	113 (37.4)	
Surgical approach			.024*
Thoracolaparoscopic	59 (56.7)	186 (61.6)	
Laparoscopic transhiatal	24 (23.1)	42 (13.9)	
Thoracolaparotomic	6 (5.8)	42 (13.9)	
Open transhiatal	12 (11.5)	20 (6.6)	
Thoracoscopic-laparotomic	3 (2.9)	12 (4.0)	
Anastomotic configuration			.649
End-to-side	102 (98.1)	298 (98.7)	
End-to-end	2 (1.9)	4 (1.3)	
Duration of surgery (minutes)	343 ± 115	361 ± 100	.121

Values are numbers of patients, with column-based percentages in parentheses or mean ± SD. * Significant difference based on χ^2 test. [a] Cardiovascular comorbidities defined as cardiac comorbidities (e.g. coronary artery bypass graft or valve replacement), vascular comorbidities (e.g. peripheral arterial disease), and/or hypertension.[b] Adenosquamous carcinoma (n=2), mixed adenoneuroendocrine carcinoma (n=2) and carcinosarcoma (n=1)

TABLE 3. Distribution of arterial calcification among patients with and without anastomotic leakage and results of univariable and multivariable logistic regression analysis with anastomotic leakage as outcome variable

Anatomical location of arterial calcification	**Score**	**Anastomotic leakage**	**No anastomotic leakage**	**Unadjusted odds-ratio** (95% CI)		**Adjusted odds-ratio*** (95% CI)	
		n=104 (25.6%)	n = 302 (74.4%)		p-value		p-value
Coronary arteries	0	31 (18.1)	140 (81.9)	reference		reference	
	1	42 (36.5)	73 (63.5)	2.60 (1.51 – 4.48)	.001	2.29 (1.28 – 4.12)	.005
	2	31 (25.8)	89 (74.2)	1.57 (0.90 – 2.76)	.116	1.29 (0.68 – 2.46)	.432
Supra-aortic arteries	0	30 (16.1)	156 (83.9)	reference		reference	
	1	25 (30.9)	56 (69.1)	2.32 (1.26 – 4.28)	.007	2.48 (1.30 – 4.74)	.006
	2	49 (35.3)	90 (64.7)	2.83 (1.68 – 4.78)	<.001	2.72 (1.49 – 4.99)	.001
Aortic valve	0	77 (25.1)	230 (74.9)	reference		reference	
	1	14 (24.1)	44 (75.9)	0.95 (0.49 – 1.83)	.879	0.86 (0.43 – 1.70)	.654
	2	13 (31.7)	28 (68.3)	1.39 (0.68 – 2.81)	.364	1.02 (0.47 – 2.19)	.968
Thoracic aorta	0	28 (19.4)	116 (80.6)	reference		reference	
	1	36 (25.4)	106 (74.6)	1.41 (0.80 – 2.46)	.232	1.37 (0.74 – 2.53)	.320
	2	40 (33.3)	80 (66.7)	2.07 (1.18 – 3.63)	.011	1.79 (0.88 – 3.67)	.110
Celiac axis	0	49 (22.1)	173 (77.9)	reference		reference	
	1	34 (29.3)	82 (70.7)	1.46 (0.88 – 2.44)	.143	1.29 (0.73 – 2.25)	.382
	2	21 (30.9)	47 (69.1)	1.58 (0.86 – 2.89)	.139	1.24 (0.62 – 2.48)	.552
Abdominal aorta	0	6 (18.2)	27 (81.8)	reference		reference	
	1	22 (18.5)	97 (81.5)	0.97 (0.36 – 2.63)	.955	0.95 (0.34 – 2.66)	.915
	2	75 (30.1)	174 (69.9)	1.87 (0.74 – 4.70)	.183	1.63 (0.58 – 4.56)	.350
	NA	1 (20.0)	4 (80.0)				
Common iliac arteries	0	9 (15.8)	48 (84.2)	reference		reference	
	1	18 (26.1)	51 (73.9)	1.68 (0.69 – 4.11)	.255	1.66 (0.66 – 4.16)	.279
	2	69 (27.3)	184 (72.7)	1.91 (0.89 – 4.09)	.098	1.71 (0.74 – 3.95)	.208
	NA	8 (29.6)	19 (70.4)				

External iliac arteries	0	50 (22.1)	176 (77.9)	reference		reference	
	1	17 (27.4)	45 (72.6)	1.42 (0.74 – 2.71)	.291	1.33 (0.68 – 2.64)	.407
	2	26 (32.1)	55 (67.9)	1.68 (0.97 – 2.92)	.066	1.47 (0.79 – 2.74)	.222
	NA	11 (29.7)	26 (70.3)				

Values in the third and fourth column represent numbers of patients, with row-based percentages in parentheses. *CI*: confidence interval; *NA*: not available. * Adjusted for age at diagnosis, BMI, history of cardiovascular disease, COPD, diabetes mellitus and smoking.

TABLE 4. Intra- and interobserver reliability and agreement of the arterial calcification scoring system per anatomical location

Anatomical location of arterial calcification	**Intraobserver**		**Interobserver**	
	Reliability (κ)[a] (95% CI)	Agreement[b] (%) (95% CI)	Reliability (κ)[a] (95% CI)	Agreement[b] (%) (95% CI)
Coronary arteries	0.63 (0.40-0.86)	73.3 (53.8-87.0)	0.86 (0.71-1.00)	90.0 (72.3-97.4)
Supra-aortic arteries	0.87 (0.74-0.99)	86.7 (68.4-95.6)	0.90 (0.79-1.00)	90.0 (72.3-97.4)
Aortic valve	0.87 (0.71-1.00)	93.3 (76.5-98.8)	0.94 (0.83-1.00)	96.7 (81.0-99.8)
Thoracic aorta	0.86 (0.73-0.99)	86.7 (68.4-95.6)	0.86 (0.73-0.99)	86.7 (68.4-95.6)
Celiac axis	0.81 (0.62-0.99)	86.7 (68.4-95.6)	0.90 (0.72-1.00)	96.7 (81.0-99.8)
Abdominal aorta	0.91 (0.79-1.00)	93.3 (76.5-98.8)	0.91 (0.78-1.00)	93.3 (76.5-98.8)
Common iliac arteries	0.96 (0.88-1.00)	96.7 (81.0-99.8)	0.88 (0.74-1.00)	90.0 (72.3-97.4)
External iliac arteries	0.96 (0.89- 1.00)	96.7 (81.0-99.8)	0.85 (0.71-0.99)	86.7 (68.4-95.6)

[a] Reliability was assessed by using Cohen's linearly weighted kappa (κ). The weighted κ statistic can be interpreted as follows: κ of 0.81 to 1.00 indicates excellent reliability; κ of 0.61 to 0.80, good reliability; κ of 0.41 to 0.60, moderate reliability; κ of 0.21 to 0.40, fair reliability; and κ of less than 0.20, poor reliability[23]. [b] Proportion of agreement between calcification scores.

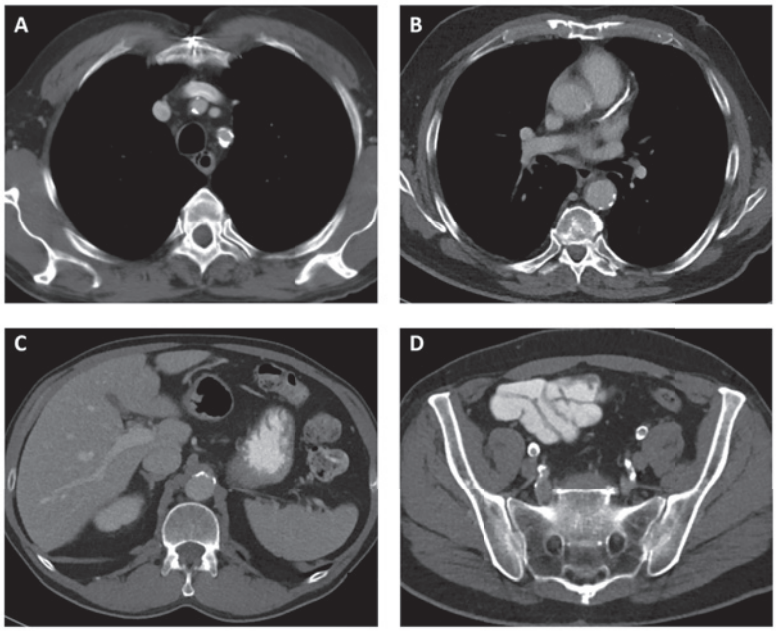

Figure 1. Examples of preoperative CT images of arterial calcification in patients with esophageal cancer. **A:** Calcification of the brachiocephalic and left subclavian artery, resulting in a score of 2 for calcification of the supra-aortic arteries. **B:** Calcification of a large segment of the left anterior descending artery, resulting in a score of 2 for calcification of coronary arteries. **C:** Calcification of the celiac axis with a maximum cross-sectional diameter of >10 mm, resulting in a score of 2 for calcification of the celiac axis. **D:** Multiple calcified foci of the internal and external iliac arteries, resulting in a score of 2 for calcification of the internal and external iliac arteries.

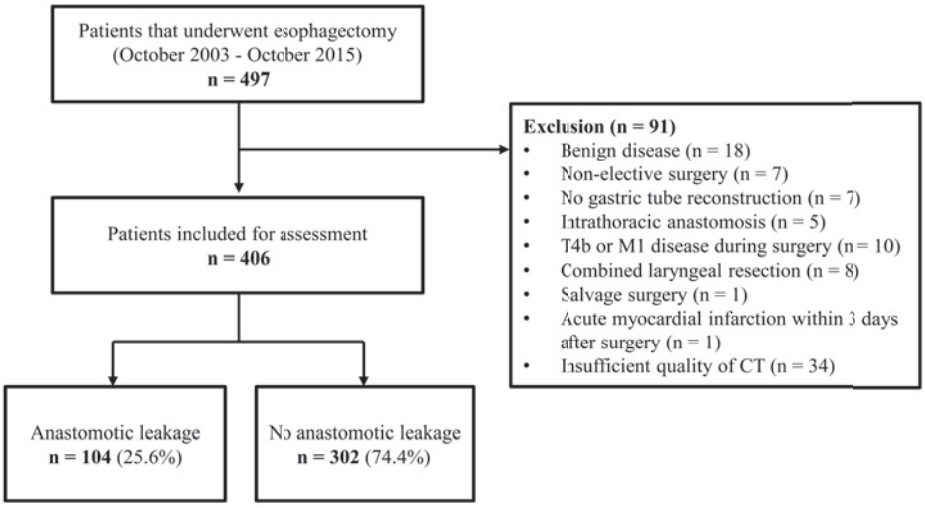

Figure 2. Flowchart of study design

DISCUSSION

Anastomotic leakage after esophagectomy remains one of the most devastating complications after esophagectomy, and has an adverse impact on prognosis[1-6,9]. Many patient and surgery-related risk factors for anastomotic leakage have been reported in literature, but fail to accurately predict the risk of anastomotic leakage. The results of this cohort study of 406 patients did not show a significant association between anastomotic leakage and characteristics such as gender, age, BMI, ASA score, cardiovascular comorbidity, diabetes mellitus and smoking. A history of COPD was the only patient-related factor significantly associated with anastomotic leakage in univariable analysis in this cohort. The chronic use of steroids by these patients has been suggested as a possible explanation for impaired anastomotic healing[2,15]. In multivariable analysis however, no standard patient-related characteristics remained significantly associated with anastomotic leakage. This highlights the multifactorial nature of anastomotic leakage and the challenging prediction of this complication.

In this study, the presence of calcification in the coronary and supra-aortic arteries was proven to be independently associated with anastomotic leakage, irrespective of clinical and treatment-related characteristics. These calcifications may be a predisposing factor or consequence of diffuse arterial disease, and could therefore be helpful to identify patients at risk for anastomotic leakage[11]. Recognition of the increased risk for developing anastomotic leakage without requiring additional imaging could aid the complex decision-making process

of surgical treatment of patients with esophageal cancer. High risk patients (e.g. patients with supra-aortic calcification score ≥ 1 have a 33.6% (74/220) risk of anastomotic leakage) could be more fully optimized before surgery by means of preventive measures to reduce their risk of anastomotic leakage. Important preoperative interventions to enhance postoperative outcome may include physical therapy to increase cardiorespiratory function and improvement of nutritional status[24-26].

To improve preoperative identification of patients at high risk for anastomotic leakage, the current study performed extensive measurements of cardiovascular features on routine preoperative CT images to explore their association with anastomotic leakage. The findings of the current study demonstrate that, not only locoregional vascular disease as demonstrated in previous studies[11,15], but also generalized vascular disease is indicative for the risk of anastomotic leakage after esophagectomy. This result adds to the current evidence of the association between atherosclerotic calcification and leakage of gastrointestinal anastomoses, which is presumably based on ischemia of the anastomosis[11,15,27-30].

In line with the ischemia hypothesis as contributing factor to the development of anastomotic leakage, it has been suggested that patients at high risk of anastomotic leakage based on their vascular status could be included in ischemic conditioning trials[10,11]. Ischemic conditioning increases perfusion of the gastric tube by partial gastric devascularization through arterial embolization or laparoscopic arterial ligation, followed by esophagectomy and anastomosis at a second stage[10]. However, currently there is insufficient evidence available to support widespread implementation of ischemic conditioning of the stomach in order to decrease anastomotic leakage rates in clinical practice[10,31]. Specifically selecting patients that are high at risk of developing anastomotic leakage (i.e. patients with minor or major arterial calcification) may improve the effect of this technique on anastomotic leakage rates[10,11].

Various limitations apply to this study. First, no internal validation of our results was performed, and external validation of our results is warranted to test the generalizability of these results in other populations (e.g. with a different prevalence of leakage, use of other surgical techniques). Second, there are some potential limitations of the visual grading system. To facilitate an easy and fast visual calcification grading system, calcification was stratified between minor and major calcification based on the number of calcified foci within a trajectory in this study. As a result, the exact number of calcified foci and their extent were not separately analyzed and thus the calcification load could vary largely within one score. Moreover, the cut off points for the number of calcifications within one score are not adjusted for a patient's

individual body height and varying anatomy of the arteries. Therefore, this simplified system could have over- or underestimated the calcification load within a patient.

Despite these potential limitations, several advantages apply to this approach. The grading system used in this study is easy to use and allows for a fast differentiation of calcification burden. This is confirmed by the high reproducibility of the calcification grading system, shown by the excellent intra- and interobserver agreement of the current and previous related studies[12,15,16]. Furthermore, for the prediction of cardiovascular events this grading system has proven to be equally efficient as more challenging scoring systems that are based on plaques or irregularities of the vascular wall[12]. Second, the scoring system does not require any special CT protocol or calcium-scoring software. Last, a CT or a combined positron emission tomography (PET)/CT scan is the principle staging tool for esophageal cancer. Obtaining information on arterial calcification therefore does not require any additional tests or imaging.

In conclusion, this study demonstrates that calcification of the coronary and supra-aortic arteries is an independent predictor of anastomotic leakage following esophagectomy. These results demonstrate that generalized vascular disease is more indicative for the risk of leakage than local vascular disease. This new described risk factor for anastomotic leakage after esophagectomy may be used in future prediction models, and eventually aid to a more individualized identification of the risk of anastomotic leakage following esophagectomy.

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Intraoperative and postoperative risk factors for anastomotic leakage and pneumonia after esophagectomy for cancer

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ABSTRACT

Objective

Morbidity and mortality after esophagectomy are often related to anastomotic leakage or pneumonia. This study aimed to assess the relationship of intraoperative and postoperative vital parameters with anastomotic leakage and pneumonia after esophagectomy.

Methods

Consecutive patients who underwent transthoracic esophagectomy with cervical anastomosis for esophageal cancer from January 2012 to December 2013 were analyzed. Univariable and multivariable logistic regression analyses were used to determine potential associations of hemodynamic and respiratory parameters with anastomotic leakage or pneumonia.

Results

From a total of 82 included patients, 19 (23%) developed anastomotic leakage and 31 (38%) experienced pneumonia. The single independent factor associated with an increased risk of anastomotic leakage in multivariable analysis included a lower minimum intraoperative pH (OR 0.85, 95% CI 0.77–0.94). An increased risk of pneumonia was associated with a lower mean arterial pressure (MAP) in the first 12 hours after surgery (OR 0.93, 95% CI 0.86–0.99) and a higher maximum intraoperative pH (OR 1.14, 95% CI 1.02–1.27). Interestingly, no differences were noted for the MAP and inotrope requirement between patients with and without anastomotic leakage.

Conclusion

A lower minimum intraoperative pH (below 7.25) is associated with an increased risk of anastomotic leakage after esophagectomy, whereas a lower postoperative average MAP (below 83 mmHg) and a higher intraoperative pH (above 7.34) increase the risk of postoperative pneumonia. These parameters indicate the importance of setting strict perioperative goals to be protected intensively.

INTRODUCTION

Surgical resection of the esophagus with en-bloc lymphadenectomy is the cornerstone of curative treatment for patients with esophageal cancer[1-3]. Anastomotic leakage and pneumonia are the most frequently encountered complications after esophagectomy[4,5]. Both complications are associated with increased postoperative morbidity, length of hospital stay and mortality[6-10]. Furthermore, both anastomotic leakage and pneumonia have been shown to negatively affect long-term cancer-specific survival after esophagectomy[11,12]. Despite improvement in surgical techniques and peri-operative management, incidence rates of up to 24-30% and 27-46% have been reported for anastomotic leakage and pulmonary complications, respectively[4,5,13].

Several factors, such as neoadjuvant chemoradiotherapy, anatomic site of the anastomosis, diabetes mellitus, body mass index (BMI), age, congestive heart failure, hypertension, renal insufficiency and smoking have been reported to contribute to the risk of anastomotic leakage or pneumonia after esophagectomy[5,7,9,14]. A reduction in tissue perfusion and subsequent oxygenation of the gastric tube is considered to be one of the main causes of insufficient anastomotic healing[6,14]. Therefore, the maintenance of vascular blood flow and adequate tissue oxygenation in the intraoperative and postoperative period are likely of importance[15,16]. Also, pulmonary complications may be related to intraoperative hypoxemia and hypotension, which trigger the release of pro-inflammatory mediators and activation of leucocytes[17]. Perioperative hypotension, decreased oxygen content and other hemodynamic and respiratory parameters are modifiable and may therefore provide potential opportunities for anastomotic and pulmonary protection intraoperatively and during the early postoperative phase at the intensive care unit (ICU).

In general, however, the influence of specific modifiable intraoperative and postoperative parameters on the occurrence of anastomotic leakage and pneumonia has not yet been elucidated. Also, clinical parameters may potentially be useful for early identification of patients who carry a high risk of developing these complications. Therefore, the aim of the current study was to evaluate associations of intraoperative and postoperative clinical parameters on the occurrence of anastomotic leakage and pneumonia after transthoracic esophagectomy in patients with esophageal cancer.

METHODS

Study population

Institutional review board approval was obtained and the requirement for written informed consent was waived for this study. All patients who underwent elective esophagectomy at

our tertiary referral center from January 2012 to December 2013 were included. Data on patient and treatment-related characteristics were extracted from a prospectively acquired surgical database. Intraoperative parameters were collected from continuously recorded digital intraoperative measurements, whereas postoperative ICU parameters were extracted from a prospectively collected ICU database.

Anesthetic procedure and postoperative analgesia

Before surgery all patients received an epidural catheter through intercostal space T5-6 or T6-7 to provide adequate intraoperative and postoperative analgesia. Pre-procedural medication consisted of prophylactic antibiotics (cefazolin 2.000 mg, metronidazole 500 mg) and intravenous injection of 10 mg/kg methylprednisolone 30 minutes prior to incision[18]. Anesthesia was performed using intravenously administered propofol, sufentanil and a muscle relaxant. Endotracheal intubation was performed with a left-sided double-lumen tube to enable desufflation of the right lung during the thoracic phase of the procedure. During single-lung ventilation, a pressure-controlled ventilation strategy was used with a maximum pressure of 27 cm H_2O and maximum tidal volume of 6 ml/kg. During double-lung ventilation, tidal volumes were set at 6-8 ml/kg with the aim to maintain end-tidal CO_2 between 40 and 45 mmHg. During the first postoperative day, epidural analgesia was maintained with a flow of 2 to 6 ml/h with 2.5 mg/ml of bupivacaine, and was not patient-controlled. In order to prevent hypotension due to vasodilatation, no further local boluses were given. In addition, all patients were provided with patient-controlled opioid analgesia.

Surgical procedure

To limit the influence of different surgical procedures on the results, only patients who underwent transthoracic resection with extended two-field lymphadenectomy were included. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy was the standard procedure for patients with esophageal cancer of all stages in our institute[19]. Exclusion criteria were benign disease and combined laryngeal resection. For the construction of the gastric tube of 4 cm wide, a linear stapling device was used and the staple line was manually oversewn (GIA™ 80, 3.8 mm, Covidien, Mansfield, MA, USA). All anastomoses were performed end-to side in the neck, using single-layer hand-sewn continuous sutures (3-0 PDS) in monolayer. After completion of the anastomosis the surplus of the gastric conduit was removed with a stapling device (GIA™ 80, 3.8 mm, Covidien, Mansfield, MA, USA). All surgical procedures were carried out by two experienced upper gastro-intestinal surgeons (JPR and RvH).

After the surgical procedure, patients were transferred to the ICU while maintaining sedation and intubation. The perfusion status of patients was routinely assessed based on the urine production, mean arterial pressure, and fluid balance. The threshold for initiating volume loading and/or epinephrine administration was set at a mean arterial pressure below 65 mmHg, or a urine production of less than 0.5 ml/kg/hour. In case of hypoperfusion volume loading was initiated with crystalloids, and/or epinephrine was administered. However, treating hypoperfusion with fluid administration was performed to a limited extent, as excessive fluid administration has shown to be a contributing factor for the development of respiratory complications after esophageal surgery[20]. Extubation was encouraged when patients were considered cardiorespiratory stable (median time to extubation was 6 hours [interquartile range (IQR)]: [1-10]). Following extubation, patients remained in the ICU until safe transfer to the surgical ward was deemed appropriate.

Variables and risk factors

Baseline parameters of interest included age, gender, BMI, American Society of Anesthesiologists (ASA) score, chronic obstructive pulmonary disease (COPD), diabetes mellitus, cardiovascular comorbidity, history of smoking and neoadjuvant treatment. The retrieved intraoperative and postoperative factors consisted of hemodynamic characteristics, respiratory characteristics, fluid management, laboratory findings and temperature. Data on postoperative management was restricted to the first 24 hours of ICU admission after surgery. Patients who were not admitted to the ICU after surgery were excluded from the analysis. A detailed description of studied factors is provided in Table 1.

Clinical leakage was defined according to the ISDE classification of anastomotic leakage, including gastrointestinal defects involving the esophagus, anastomosis, staple line or gastric tube[21,22]. Clinical leakage included visualization of anastomotic dehiscence or fistulae during endoscopy, visible loss of saliva through the cervical wound, or sepsis caused by mediastinal or intrathoracic manifestations confirmed by CT scan. Radiological leakage was defined as extravasation of water-soluble contrast during a barium swallow study or computed tomography (CT) scan. Both clinical and radiological anastomotic leakages were scored within 30 days after surgery. Postoperative pneumonia was defined according to the definition of the Utrecht Pneumonia Score (UPS)[23]. In this clinical scoring system points are assigned based on leukocyte count, temperature and radiography findings. Pneumonia is defined as a score of minimally 2 points, with at least 1 point for pulmonary radiography (i.e. findings of either diffused or well-circumscribed infiltrate).

Statistical analysis

Multiple imputation of missing values was performed to deal with missing values for intraoperative and postoperative clinical parameters, using 20 imputed datasets[24]. The association of patient and treatment-related factors with anastomotic leakage and pneumonia was studied univariably. Categorical parameters were compared using the Chi-square test or Fisher's exact test in case of small cell counts. The Student's T-test and Mann-Whitney U test were used to compare groups with and without anastomotic leakage and with or without pneumonia for parametric and non-parametric continuous parameters, respectively. In order to analyze whether the different intraoperative and postoperative clinical parameters influenced the risk of anastomotic leakage and pneumonia, univariable logistic regression models were constructed providing odds ratios (ORs) with 95% confidence intervals (CIs). Logarithmic transformations were applied for several parameters to achieve improved linearity on the log odds scale. Also, for several parameters the values were multiplied by 100 to facilitate an easier interpretation of the OR estimates.

Subsequently, parameters with a $p \leq 0.10$ in univariable analysis were entered in a multivariable logistic regression model to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage or pneumonia. High correlations between some parameters were expected (e.g. pCO_2 and pH), resulting in the statistical problem of (multi) collinearity. Therefore, from highly correlated pairs of parameters (i.e. Spearman rank correlation coefficient $r \geq 0.6$) only the one parameter with the lowest *p*-value in univariable analysis was pre-selected for the multivariable model. For parameters that remained independently and significantly related to anastomotic leakage or pneumonia, receiver operating characteristic (ROC) curve analyses were performed to determine ideal cut-off values by giving equal weight to sensitivity and specificity. Statistical analysis was performed using SPSS 20.0 (IBM Corp. Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

TABLE 1. Studied intraoperative and clinical parameters

Intraoperative factors	Postoperative factors (first 24 hours)
Hemodynamic factors	
Duration of surgery (minutes)	First postoperative systolic RR† (6.1% imputed)
Blood loss (mL)	First postoperative diastolic RR† (1.2% imputed)
Minimum hemoglobin measured	Average MAP at different time points* † (6.1% imputed)
Number of blood transfusions	Total duration MAP <60 (minutes)
Inotrope requirement (yes or no)	Total duration systolic RR < 90 (minutes)
Maximum inotrope dose in mg/h	Inotrope requirement (yes or no)
Time in minutes of inotrope admission	Maximum inotrope dose in mg/h
Minimum measured MAP	Total duration inotrope requirement (minutes)
Time in minutes that systolic RR was <90	Inotrope requirement at different time points*
Time in minutes that MAP was <60	Urine production (mL) at different time points*† (6.1% imputed)
Diuresis <30cc/h (yes or no)	First measured postoperative hemoglobin
Maximum measured heart rate	Fluid balance (mL) 0-6, 0-12,0-18 hours after surgery† (8.5% imputed)
Minimum measured heart rate	Diuresis <30cc/h (yes or no)
Average heart rate	
Total fluid infusion (mL)	
Average diuresis (mL/h)	
Respiratory factors	
Duration one-lung ventilation (minutes)	Mean respiratory rate
Average saturation	Average saturation
Minimum FiO_2	pO_2/FiO_2 ratio
Maximum FiO_2	Time to extubation (minutes)† (1.2% imputed)
Average FiO_2	First ABG pH
Maximum pH in ABG† (7.3% imputed)	First ABG pCO_2
Minimum pH ABG † (7.3% imputed)	First ABG pO_2
pH <7.36 (yes/no)† (7.3% imputed)	First ABG bicarbonate
Maximum ABG pCO† (7.3% imputed)	First ABG base excess
Minimum ABG pCO_2†(7.3% imputed)	
Maximum ABG pO_2† (7.3% imputed)	
Minimum ABG pO_2† (7.3% imputed)	
Maximum ABG bicarbonate† (7.3% imputed)	
Minimum ABG bicarbonate† (7.3% imputed)	
Average PEEP	
Mean tidal volumes	
Other factors	
Average temperature measured	First postoperative temperature measured
Minimum temperature measured	Maximum temperature measured
Maximum temperature measured	

*Different time points: 0-6, 7-12, 13-18,19-24, 0-12, 13-24 and 0-24 hours after surgery. RR: blood pressure. MAP: mean arterial pressure. ABG: arterial blood gas. mL: milliliter. h: hour. †Imputed variables.

RESULTS

In the study period a total of 106 patients underwent esophagectomy with gastric tube reconstruction. Of these patients, 24 were excluded because of a transhiatal resection (n=15), benign disease (n=4), insufficient recording of postoperative data due to admission to the post anesthesia care unit instead of the ICU (n=3), or a combination with laryngeal resection (n=2). In 19 (23%) of the remaining 82 patients anastomotic leakage occurred, whereas 31 patients (38%) experienced postoperative pneumonia. Anastomotic leakage occurred after a median time of 8 days (range 3-17) after esophagectomy, whereas pneumonia was diagnosed after a median of 5 days (range 2-18). Treatment of anastomotic leakage consisted of ceasing oral intake in combination with opening of the cervical wound (n=3, type 1 leakage), placing a stent (n=1, type 2 leakage) or surgical re-intervention (n=14, type 3 leakage). Missing values were encountered for 15 variables, but the percentage of missing values per variable was limited (median 6%, range 1% to 9%). Imputed variables with their percentages missing values are highlighted in Table 1.

The median length of hospital stay was prolonged in patients with anastomotic leakage compared to patients without anastomotic leakage (median [IQR]: 27 days [21-33] versus 13 days [11-18], respectively; $p<0.001$). Also, in patients with pneumonia the length of hospital stay was increased compared to patients without pneumonia (median [IQR]: 19 days [13-35] versus 13 days [10-18], respectively; $p<0.001$). In-hospital mortality occurred in 3 (3.7%) of 82 patients, of which 2 suffered from both pneumonia and anastomotic leakage. Simultaneous occurrence of anastomotic leakage and pneumonia within the same individual was found in 7 of 82 patients (8.5%). No significant difference in incidence of pneumonia among patients with or without anastomotic leakage was found (37% versus 38%, respectively: $p=0.572$*).*

Patient and treatment-related characteristics and their univariable association with anastomotic leakage and pneumonia are demonstrated in Table 2. COPD was relatively rare (n=4), but significantly related to a higher risk of anastomotic leakage ($p=0.037$). Other studied patient and treatment-related factors were not significantly associated with the occurrence of either anastomotic leakage or pneumonia.

Anastomotic leakage

Intraoperative and postoperative clinical parameters that showed a potential association with anastomotic leakage in univariable analysis ($p\leq0.10$) are presented in Table 3. In univariable analyses studying intraoperative factors a lower minimum pH, lower maximum pH, higher pCO_2, and higher minimum pCO_2 in the arterial blood gas (ABG) were significantly associated

with an increased risk of anastomotic leakage. Postoperatively on the ICU, a higher pCO_2 in the first postoperative ABG after esophagectomy was significantly associated with an increased risk of anastomotic leakage. No other intraoperative and postoperative clinical parameters were significantly associated with anastomotic leakage (Online Supplement 1-3). Specifically, no differences between patients with and without leakage were noted for the mean arterial pressure (MAP) and duration of inotrope requirement (in the form of noradrenaline).

In multivariable analysis, a lower intraoperative minimum pH remained independently associated with a higher risk of anastomotic leakage (OR 0.85 [per 0.01 increase in pH], 95% CI 0.77–0.94, p=0.003; Table 4). Using ROC analysis the minimum pH below which the risk of anastomotic leakage increased significantly was statistically determined at 7.25 (Table 6). Patients with a pH below versus above this threshold had a chance of 51% versus 12% to develop anastomotic leakage, respectively (Table 6, Figure 1). The intraoperative minimum pH was measured during the thoracic phase, before gastric mobilization and gastric tube construction in 65% of all patients. To the contrary, the minimum pH was measured during gastric mobilization or after gastric tube reconstruction in only 13% and 22% of patients, respectively. The surgical phase in which the minimum pH was measured did not significantly influence the risk of anastomotic leakage (p=0.444).The first postoperative pCO_2 did not retain its significant association with anastomotic leakage when adjusted for intraoperative minimum pH.

Pneumonia

Parameters that showed a potential association with the development of pneumonia in univariable analysis ($p \leq 0.10$) are presented in Table 5. In univariable analysis, patients with postoperative pneumonia had a significantly higher maximum pH and lower minimum pCO_2 in the intraoperative ABG measurements. Postoperative ICU parameters associated with pneumonia included a lower average MAP in the first 6, 12 and 24 hours after surgery and a urine production of less than 30 mL during at least one hour in the first 24 hours after surgery. No other intraoperative and postoperative clinical parameters were significantly associated with pneumonia (Online Supplement 1-3). Specifically, no differences between patients with and without pneumonia were noted with regard to the time to extubation after surgery.

The maximum intraoperative pH, intraoperative blood loss, average MAP between 0 to 12 hours postoperatively and postoperative urine production of <30 mL during at least one hour in the first 24 hours were selected for multivariable analysis (Table 4). Higher maximum intraoperative pH (OR 1.14 [per 0.01 increase in pH], 95% CI 1.02–1.27, p=0.024) and lower

average MAP (OR 0.93, 95% CI 0.86–0.99, p=0.035) in the first 12 hours after esophagectomy on the ICU remained independently associated with pneumonia. Using ROC analysis, the maximum intraoperative pH above which the risk of pneumonia increased significantly was statistically determined at 7.34. Patients with a maximum intraoperative pH above versus below this threshold had a chance of 52% versus 23% to develop pneumonia, respectively (Table 6, Figure 1). The maximum intraoperative pH was measured during the thoracic phase, gastric mobilization, and after gastric tube reconstruction, in 21%, 42%, and 37% of patients, respectively. The surgical phase in which the maximum pH was measured did not significantly influence the risk of pneumonia (p=0.422). The average postoperative MAP (0-12 hours) below which the risk of pneumonia increased significantly was identified at 83 mmHg. Patients with an average postoperative MAP (0-12 hours) below versus above this threshold had a chance of 49% versus 9% to develop pneumonia after esophagectomy, respectively (Table 6, Figure 1). Postoperative urine production of <30 mL during at least 1 hour in the first 24 hours and intraoperative blood loss did not retain their significant association with pneumonia when adjusted for the maximum intraoperative pH and average MAP in the first 12 hours after esophagectomy.

TABLE 2 Patient and treatment-related characteristics in relation to postoperative complications

Characteristic	No anastomotic leakage (n=63)	Anastomotic leakage (n=19)	*p* value	No pneumonia (n=51)	Pneumonia (n=31)	*p* value
Male gender	50 (79.4)	14 (73.7)	0.752	39 (76.5)	25 (80.6)	0.658
Age (years)*	63.0 ± 9.0	63.9 ± 6.8	0.813	63.6± 8.4	62.5 ± 8.8	0.569
BMI (kg/m^2)*	25.1 ± 3.3	25.4 ± 5.3	0.987	25.3 ± 3.9	24.9 ± 3.5	0.382
ASA score			0.505			0.147
I	17 (27.0)	3 (15.8)		9 (17.6)	11 (35.5)	
II	34 (54.0)	13 (68.4)		33 (64.7)	14 (45.2)	
III	12 (19.0)	3 (15.8)		9 (17.6)	6 (19.4)	
COPD	1 (1.6)	3 (15.8)	0.037	1 (2.0)	3 (9.7)	0.116
FEV_1 predicted	102.7 ± 16.1	99.7 ± 22.0	0.286	103.5 ± 17.4	99.6 ± 17.8	0.840
Cardiac co-morbidity	20 (31.7)	5 (26.3)	0.652	12 (23.5)	13 (41.9)	0.079
Vascular co-morbidity	24 (38.7)	8 (41.1)	0.791	19 (38.0)	13 (41.9)	0.725
Diabetes mellitus	6 (9.5)	3 (15.8)	0.426	3 (5.9)	6 (19.4)	0.076
Smoking at diagnosis	15 (23.8)	1 (5.3)	0.101	8 (15.7)	8 (25.8)	0.262
Neoadjuvant therapy			0.314			0.225
No therapy	8 (12.7)	1 (5.3)		4 (7.8)	5 (16.1)	
Chemotherapy	12 (19.0)	5 (26.3)		13 (25.5)	4 (12.9)	
Chemoradiotherapy	43 (68.3)	13 (68.4)		34 (66.7)	22 (71.0)	

Data presented as numbers of patients with percentages in parentheses. *Data presented as mean ± standard deviation. Cardiac co-morbidity: history of myocardial infarction, heart failure, cardiac arrhythmia, or (treated) coronary artery disease. Vascular co-morbidity: history of hypertension or peripheral artery disease.

TABLE 3 Univariable analyses of intraoperative and postoperative clinical parameters potentially associated with anastomotic leakage ($p \leq 0.10$)

Parameter	No anastomotic leakage	Anastomotic leakage	OR	95% CI	*p* value
Intraoperative					
Maximum pH in ABG*	7.36 [7.32-7.39]	7.33 [7.27-7.36]	0.880	0.789 - 0.980	0.020
Minimum pH in ABG*	7.30 [7.27-7.35]	7.22 [7.15-7.30]	0.847	0.767 - 0.934	0.001
Maximum pCO_2 in ABG	52.0 [46.0-56.0]	65.0 [50.0-76.0]	1.091	1.032 - 1.125	0.002
Minimum pCO_2 in ABG	43.0 [39.3-46.0]	46.0 [40.0-53.0]	1.112	1.024 - 1.206	0.011
Postoperative					
pH in first postoperative ABG*	7.38 [7.35-7.41]	7.35 [7.33-7.38]	0.907	0.818 - 1.006	0.063
pCO_2 in first postoperative ABG*	41.0 [36.0-46.0]	44.0 [38.0-52.0]	1.100	1.006 - 1.203	0.036

Data presented as median with interquartile range [IQR] between brackets. *Note* – Only factors showing a potential association ($p \leq 0.10$) with the outcome are presented. ABG: arterial blood gas. CI: confidence interval. OR: Odds ratio. *Parameter multiplied by 100 to facilitate interpretation of the OR.

TABLE 4 Results of multivariable logistic regression analysis

Parameter	OR	95% CI	*p* value
Anastomotic leakage			
Intraoperative minimum pH in ABG*	0.848	0.766 - 0.939	0.001
pCO_2 in first postoperative ABG	1.091	0.989 - 1.204	0.083
Pneumonia			
Postoperative MAP 0-12h	0.927	0.864 - 0.995	0.035
Intraoperative maximum pH in ABG*	1.136	1.017 - 1.269	0.024
Postoperative diuresis <30 mL/h	1.931	0.584 - 6.384	0.281
Intraoperative blood loss (mL)†	1.000	0.999 - 1.000	0.362

ABG: arterial blood gas. CI: confidence interval. OR: odds ratio. MAP: mean arterial pressure. mL: milliliter. †Log-transformed parameter. *Parameter multiplied by 100 to facilitate interpretation of the OR.

TABLE 5 Univariable analyses of intraoperative and postoperative clinical parameters potentially associated with pneumonia ($p \leq 0.10$)

Parameter	No pneumonia	Pneumonia	OR	95% CI	*p* value
Intraoperative					
Blood loss (mL)†	360 [200-580]	460 [340-810]	1.672	0.939 - 2.977	0.081
Maximum pH in ABG*	7.34 (7.30-7.37)	7.37 (7.34-7.40)	1.152	1.034 - 1.283	0.010
Minimum pCO_2 in ABG	45.0 (42.0-49.0)	39.0 (39.0-45.0)	0.919	0.845 - 1.000	0.050
Postoperative					
Average MAP 0-6h	79.1 (75.0-86.7)	77.4 (71.7-80.3)	0.941	0.889 - 0.997	0.039
Average MAP 7-12h	78.4 (71.5-92.1)	74.5 (68.7-81.1)	0.936	0.887 - 0.986	0.013
Average MAP 13-18h	83.2 (74.2-95.2)	80.0 (71.8-82.8)	0.961	0.924 - 1.000	0.050
Average MAP 13-24h	81.4 (72.3-97.2)	82.7 (72.6-88-2)	0.966	0.927 - 1.006	0.092
Average MAP 0-12h	77.5 (73.6-87.8)	75.8 (72.8-78.5)	0.917	0.858 - 0.980	0.011
Average MAP 0-24h	79.3 (75.7-90.6)	77.8 (70.9-81.8)	0.938	0.888 - 0.992	0.025
Diuresis <30 mL/h (yes/no)	30 (58.8%)	25 (80.1%)	3.215	1.070 - 9.660	0.037

ABG: arterial blood gas. CI: confidence interval, h: hour. MAP: mean arterial pressure. OR: odds ratio. †Log-transformed parameter. *Parameter multiplied by 100 to facilitate interpretation of the OR.

TABLE 6 Diagnostic performance of vital parameters resulting from multivariable analysis for predicting the postoperative complications

	Outcome				
Parameter	**Ideal cut-off**	**SE(%)**	**SP(%)**	**PPV(%)**	**NPV(%)**
Anastomotic leakage					
Intraoperative minimum pH in ABG	7.25	63.9	81.4	51.0	88.1
Pneumonia					
Average MAP 0-12h	83.21	93.5	41.1	49.1	91.3
Intraoperative maximum pH in ABG	7.34	70.0	59.9	51.5	76.7

MAP: mean arterial pressure. ABG: arterial blood gas. SE: sensitivity. SP: specificity. PPV: positive predictive value. NPV: negative predictive value.

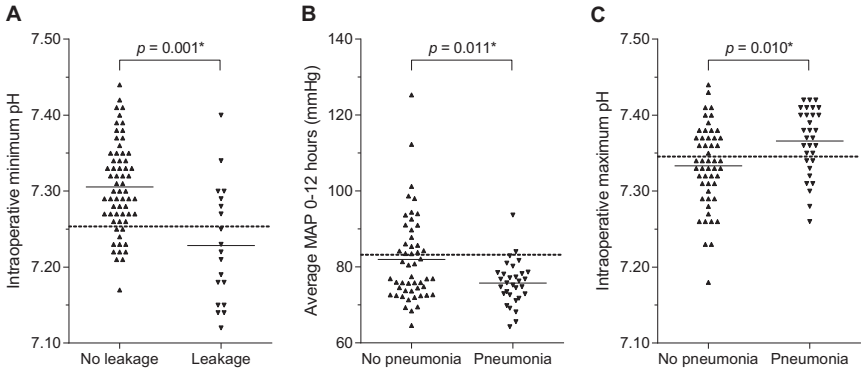

Figure 1. Scatter plots demonstrating the difference in intraoperative minimum pH between patients with and without anastomotic leakage (A), average MAP (mmHg) in the first 12 hours after surgery (B), and intraoperative maximum pH (C) between patients with and without pneumonia. Horizontal continuous and dotted lines represent group means and optimal cut-off levels, respectively.

DISCUSSION

Recognition of the influence of intraoperative and postoperative clinical parameters on the occurrence of the two most frequently encountered complications after esophagectomy for cancer could contribute to the improvement of intraoperative and postoperative decision-making and development of preventative therapeutic approaches. However, so far these influences have not yet been analyzed in detail. In this study extensive measurements of hemodynamic and respiratory factors during and early after esophagectomy were performed to investigate the association of these factors with postoperative anastomotic leakage and pneumonia. A lower minimum intraoperative pH (below 7.25) was found to be significantly associated with anastomotic leakage, whereas a higher intraoperative pH (above 7.34) and a lower average MAP (below 83 mmHg) in the first 12 hours after esophagectomy were significantly and independently related to pneumonia. These findings may be used to set and protect specific perioperative cardiorespiratory goals that may lead to reduced postoperative complications.

Previous studies have identified blood loss during surgery[25], hypotensive events[25], insufficient oxygen delivery[26] and the need for inotropic support[27] as perioperative risk factors for anastomotic leakage after esophagectomy. In the current study no differences between patients with and without for anastomotic leakage with regard to perioperative MAP measurements, intraoperative blood loss and the need for inotropic support between patients with and

without for anastomotic leakage were observed. However, a lower minimum intraoperative pH was identified as independent risk factor for anastomotic leakage. The intraoperative pH may be an indicator of surgical stress and the patient's physical reserve, since a low pH can frequently be attributed to hypovolemia and tissue hypoperfusion[28]. Tissue hypoperfusion is often associated with hypotension and hypoxemia. Hypoxemia and poor tissue perfusion have previously been considered as major causes of anastomotic leakage[6,14,26]. The current study rather suggests that intraoperative pH measurement may serve as a better predictor for the occurrence of anastomotic leakage compared to parameters related to blood pressure and blood loss. Interestingly, the surgical phase in which the minimum intraoperative pH occurred was independed of the risk of anastomotic leakage.

Our study demonstrated that a lower average MAP in the first 12 hours after surgery was independently associated with a higher risk of pneumonia. This observation corresponds with the results of a previous study that found an association between hypotension and respiratory complications after esophagectomy[17]. Perioperative hypotension has been linked to the release of pro-inflammatory mediators and activation of circulating neutrophils[17,29]. This inflammatory response can cause lung injury by damaging the endothelial and epithelial cells, which predicted the occurrence of pulmonary complications in another study[30]. The development of lung injury caused by the described chain of events may contribute to the development of postoperative pneumonia. In addition, a higher pH in the intraoperative ABG was found to be associated with an increased risk of developing pneumonia. The higher pH in these patients was accompanied by lower pCO_2 values in these patients, which may suggest ventilation-induced hypocapnia. This might in turn be a consequence of relatively high ventilation frequency or high tidal volumes applied during intraoperative ventilation which can cause ventilation-induced lung injury[31,32]. However, we were not able to substantiate this hypothesis since both higher intraoperative tidal volumes, higher positive end-expiratory pressure (PEEP) and higher ventilation frequencies were not associated with pneumonia (Online Supplement 2). Other factors that have been associated with postoperative pulmonary complications in previous studies include increased infusion of crystalloid and colloids, the use of inotropics and the impairment of pO_2/FiO_2[17,29,30]. These associations could not be confirmed by the current study, but we reasonably assume that at least to some extent these parameters are related to blood pressure and ABG measurements that did appear influential in this study.

Understanding the mechanism associated with the development of anastomotic leakage and pneumonia is of importance, since this may lead to prevention and earlier diagnosis of these potentially fatal complications. In the current series, the parameters associated

with anastomotic leakage and pneumonia were likely related to a state of cardiorespiratory instability. It remains unclear whether the association is causal, or if the parameters merely represent a compromised physiologic state associated with an increased risk of anastomotic leakage and pneumonia. Therefore, further investigations are indicated to evaluate the effect of hemodynamic and respiratory interventions, during and after esophagectomy on the postoperative course.

Postoperative anastomotic leakage was relatively common in the current series, occurring in 22% of the patients. Although this appears higher than some other studies, our definition of anastomotic leakage is rather unrestrictive including basically any sign of clinical or radiological evidence of leakage. Furthermore, the leakage rate in this study appears to be comparable to the leakage rates of 22% and 30% that were reported in the recent multicenter randomized controlled CROSS-trial[4].

Certain limitations apply to this study. First, the study was single centered and included a relatively small sample size. Second, this is a hypothesis-generating observational study, and therefore the identified associations with anastomotic leakage and pneumonia cannot provide inference of causality. Given the exploratory nature of the study we did not adjust for multiple testing, and therefore false-positive findings cannot be excluded.

In conclusion, this study provides an elaborative means of investigating the possible association of intraoperative and postoperative clinical parameters with anastomotic leakage and pneumonia in patients undergoing esophagectomy for cancer. Intraoperative lower minimum arterial pH (below 7.25) was associated with the development of anastomotic leakage. A lower postoperative average mean arterial pressure (below 83 mmHg) and a higher maximum intraoperative pH (above 7.34) were associated with the development of postoperative pneumonia. These findings may lead to protocols that set goals to provide for better perioperative cardiorespiratory management reducing postoperative complications. Further investigations are indicated to evaluate the effect of hemodynamic and respiratory interventions during and after esophagectomy on the occurrence of anastomotic leakage and pneumonia and elucidate causality and non-causality of the found associations.

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Perioperative chemotherapy versus neoadjuvant chemoradiotherapy for esophageal or gastroesophageal junction adenocarcinoma: a propensity score-matched analysis comparing toxicity, pathologic outcome, and survival

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ABSTRACT

Objective

To evaluate toxicity, pathologic outcome, and survival after perioperative chemotherapy (pCT) compared to neoadjuvant chemoradiotherapy (nCRT) followed by surgery for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma.

Methods

Consecutive patients with resectable esophageal or GEJ adenocarcinoma who underwent pCT (epirubicin, cisplatin and capecitabine) or nCRT (paclitaxel, carboplatin, and 41.4 Gy) followed by surgery in a tertiary referral center in the Netherlands were compared. Propensity score matching was applied to create comparable groups.

Results

Of 193 eligible patients, 21 were discarded after propensity score matching; 86 and 86 patients who underwent pCT and nCRT, respectively, remained. Grade ≥3 thromboembolic events occurred only in the pCT group (19% vs. 0%, $p<0.001$), whereas grade ≥3 leukopenia occurred more frequently in the nCRT group (14% vs. 4%, $p=0.015$). No significant differences regarding postoperative morbidity and mortality were found. Pathologic complete response was more frequently observed with nCRT (18% vs. 11%, $p<0.001$), without significantly improving radicality rates (95% vs. 89%, $p=0.149$). Both strategies resulted in comparable 3-year progression-free survival (pCT vs. nCRT: 46% vs. 55%, $p=0.344$) and overall survival rates (49% vs. 50%, $p=0.934$). At 3-year follow-up, fewer locoregional disease progression occurred in the nCRT group (19% vs. 37%, $p=0.024$).

Conclusion

Compared to perioperative chemotherapy, neoadjuvant chemoradiotherapy achieves higher pathologic response rates and a lower risk of locoregional disease progression, without improving survival.

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide, and the incidence of esophageal adenocarcinoma is rapidly increasing[1,2]. Resection of the esophagus with en-bloc lymphadenectomy is the mainstay of curative treatment for patients with esophageal cancer[3]. However, a multimodality treatment approach is increasingly utilized since both perioperative chemotherapy (pCT) and neoadjuvant chemoradiotherapy (nCRT) have shown a survival benefit over surgery alone[4-7]. Response to neoadjuvant treatment has been associated with a higher percentage of radical surgical resection rates (R0), a reduced risk of tumor recurrence, and improved overall survival rates[8-10]. Currently, the optimal multimodality treatment strategy for resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma has not been established[5,11].

The use of perioperative chemotherapy for esophageal cancer has yielded varying outcomes in terms of toxicity, pathologic outcome, and survival[12-14]. The MAGIC-trial showed a significant benefit of perioperative epirubicin, cisplatin, and fluorouracil chemotherapy over surgery alone with regard to R0 resection rates and survival[4]. Consecutive studies found that oral capecitabine was as effective as fluorouracil in this group of patients[15,16]. Nevertheless, these treatment regimens are associated with a high toxicity profile, mainly consisting of thromboembolic events[4,17]. In the recent CROSS trial, chemoradiotherapy followed by surgery was compared to surgery alone for patients with resectable esophageal cancer[10]. This trial recorded significantly increased R0 and survival rates, and achieved a significant rate of pathologic complete response (pathCR), favoring the multimodality group. This improvement was found to be clinically relevant for both squamous cell carcinoma and adenocarcinoma[6]. Due to the relatively low percentage of adverse events in combination with improved oncologic results, neoadjuvant chemoradiotherapy followed by surgery is now the preferred treatment strategy in the U.S. National Comprehensive Cancer Network (NCCN) guidelines[18]. Meanwhile, perioperative chemotherapy remains the preferred treatment option for resectable esophageal or GEJ adenocarcinoma according to the British Society of Gastroenterology guidelines[19].

Currently, direct comparisons between perioperative chemotherapy with epirubicin, cisplatin and capecitabine (ECC) and neoadjuvant chemoradiotherapy consisting of paclitaxel, carboplatin and concurrent radiotherapy (CROSS) for patients with esophageal or GEJ adenocarcinoma are limited. Therefore, the current study aimed to compare these two treatment regimens with regard to toxicity, pathologic outcome, and survival.

METHODS

Patient population

From a prospectively acquired database consecutive patients treated with perioperative ECC or preoperative nCRT according to CROSS with the intention to receive surgery for resectable esophageal or GEJ adenocarcinoma (Siewert type I and II) were analyzed. Patients were treated between October 2006 and September 2015 at our tertiary referral center. In May 2012 the standard treatment with curative intent was switched from perioperative chemotherapy to neoadjuvant chemoradiotherapy. Diagnostic work-up consisted of endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT scanning for clinical staging. All patients had a WHO performance status of 0-2 and biopsy-proven resectable adenocarcinoma (clinical stage T1N1-3 or T2-4aN0-3) with no evidence of distant metastases at initial staging.

Treatment protocols

Chemotherapy consisted of pre- and postoperative three-week cycles of an intravenous bolus of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2), followed by 625 mg/m^2 of capecitabine twice daily for 21 days[17]. The chemoradiotherapy regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks with concurrent weekly administration of carboplatin (targeted at an area under the curve of 2 mg/ml per minute) and paclitaxel (50 mg/m^2 of body-surface area)[10]. After completion of neoadjuvant treatment, patients were scheduled for transthoracic esophagectomy with en-bloc two-field lymphadenectomy followed by gastric conduit reconstruction with cervical anastomosis end-to-side with hand-sewn continuous sutures in monolayer[20]. Patients with severe cardiopulmonary co-morbidity were scheduled for a transhiatal esophagectomy as the risk of complications associated with a transthoracic resection was considered too high.

Data collection and follow-up

Clinical patient characteristics, treatment details (e.g. chemotherapy regimens, surgical approach) and surgical outcome data (e.g. anastomotic leakage, hospital stay) were collected from the prospectively maintained database. Grading of toxicity was performed retrospectively by two independent observers according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0[21]. After esophagectomy, patients were routinely followed with an interval of 3 months in the first year, 6 months during the second year, and 12 months until 5 years after surgery. Diagnostic imaging was only performed in case of clinically suspected tumor recurrence. Recurrence was confirmed by histology or by

clinical follow-up. Locoregional recurrence was defined as recurrence at the anastomotic site, mediastinum or upper abdomen, while distant recurrence was defined as recurrence in distant organs or distant lymph nodes. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of first chemotherapy infusion to either the date of recurrence or last follow-up, or the date of death or last follow-up, respectively. Death from non-disease-related causes (e.g. myocardial infarction) were censored in the PFS analysis.

Postoperative course

Postoperative complications were graded according to the Clavien-Dindo classification[22, 23]. Definitions of the reported complications are presented in Table 3. Postoperative complications were prospectively registered and discussed weekly.

Pathological analysis

The resected specimens were processed according to a standardized protocol in accordance with the 7th edition of the International Union Against Cancer for ypTNM-classification[24]. The (circumferential) resection margin was evaluated using the College of American Pathologist criteria[25]. The degree of histopathologic tumor regression was graded according to the system proposed by Mandard et al[26].

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages). To evaluate significance of differences between the two groups, the chi-square test was used for categorical variables, and the Student's T-test and Mann-Whitney U-test were used for parametric and non-parametric continuous variables, respectively. Overall survival and PFS were assessed using the Kaplan-Meier method, with the log-rank test to determine significance. A p-value of <0.05 was considered statistically significant.

To reduce the effect of confounding influences of covariates on the assessed outcome between the two study groups (pCT versus nCRT), propensity score matching was used to build comparable groups. First, a propensity score (the probability [ranging from 0 to 1] that a patient was assigned to the chemotherapy or chemoradiotherapy group given the individual profile of potential confounders) was calculated for each patient using logistic regression, based on all covariates (n=9) marked in Table 1. Next, propensity score matching with the 'optimal matching' technique was used to generate matched pairs of cases (1:1) in which the average

within-pair difference in propensity scores was minimized[27]. Patients who fell outside the joint range of propensity scores (i.e. range of common support) were discarded.

RESULTS

Patient characteristics

In the study period a total of 106 patients underwent pCT and 87 underwent nCRT. In the original cohort differences were observed regarding patient and treatment-related characteristics. Using propensity score matching, 86 chemotherapy and 86 chemoradiotherapy patients could be matched without large imbalances of the used covariates. After propensity score matching balance among the two treatment arms improved substantially (Table 1). The results of the propensity score-matched cohort will be discussed here in further detail as this cohort consisted of groups with improved comparability.

Toxicity

A total of 66 out of 86 patients (79%) received the complete treatment regimen of three preoperative chemotherapy cycles. Postoperative continuation of chemotherapy was administered in 34 patients (40%). The 5 cycles of chemotherapy within the nCRT group were completed in 63 of 86 patients (73%), whereas 85 (99%) received all 23 fractions of radiotherapy. The main reason for not completing all chemotherapy cycles in the nCRT group was leukopenia. Grade ≥3 adverse events in the pCT group mainly consisted of clinically relevant thromboembolic events, which occurred only in the pCT group and not in the nCRT group (19 vs. 0%, $p<0.001$), 9 of which were symptomatic pulmonary emboli. The remaining 7 thromboembolic evens were asymptomatic (aortic or pulmonary emboli) and were detected during follow-up CT scans. Also grade ≥3 diarrhea occurred only in the chemotherapy group (8 vs. 0%, $p=0.014$). On the contrary, the incidence of grade ≥3 leukopenia in the nCRT group was significantly higher than observed in the chemotherapy group (14% vs. 4%, p=0.015). Other preoperative grade ≥3 adverse events did not differ significantly between the chemotherapy and chemoradiotherapy group (Table 2).

After surgery 34 (40%) of the patients in the pCT group started with adjuvant chemotherapy. The reason why 60% of the patients did not start the intended postoperative therapy was predominantly due to early cessation of the preoperative chemotherapy (n=20), postoperative complications or difficulty with recovery after surgery (n=20), postoperative mortality (n=3), disease progression (n=7), or patient decision (n=2). There were no statistical differences in preoperative patient-related characteristics, and tumor characteristics between patients who did and did not undergo postoperative chemotherapy.

Postoperative course

In the chemotherapy group, 84 of 86 (98%) patients underwent esophageal resection, compared to 84 of 86 (98%) in the chemoradiotherapy group. Reasons to refrain from resection were disease progression during therapy (1 patient in the pCT group) and diagnosis of metastatic disease during surgery (1 patient in the pCT group and 2 patients in the nCRT group). Surgical results and postoperative complications are demonstrated in Table 3. In the pCT group, a complicated postoperative course occurred in 58 of 84 patients (69%), whereas in the nCRT group 61 of 84 patients (73%) had a complicated course (p=0.661). Severity and incidences of specific postoperative complications were comparable between both groups. Also, duration of hospital stay and postoperative 30-day mortality were comparable. In the pCT group, 5 of 84 (6%) patients died within 90 days after surgery, compared to 6 of 84 (7%), in the nCRT group (p=0.755). Of the 5 deaths in the pCT group 3 died due to postoperative complications and 2 patients died due to rapid-tumor progression without severe postoperative complications. In the nCRT group all 6 patients died due to severe postoperative complications.

Pathological assessment

Pathologic results are presented in Table 4. A pathCR was more frequently observed in patients who underwent nCRT compared to pCT (18% vs. 11%, respectively, p<0.001). Also a good response (Mandard 1 and 2) occurred more often in the nCRT group compared to the pCT group (37% vs. 17%, p=0.003). An R0 resection was achieved in 75 of 84 surgical patients (89%) in the chemotherapy group, compared to 80 of 84 (95%) in the chemoradiotherapy group (p=0.149).

Survival

In the intention-to-treat analysis (including all patients who did and did not undergo surgical resection after propensity score matching), median follow-up was 34 months (range 2-97) in the pCT group and 21 months (range 3-47) in the nCRT group, respectively. At 3 years follow-up, OS (49% vs. 50%; log-rank test p=0.934) and PFS (46% vs. 55%; log-rank test p=0.344) were comparable between the pCT and nCRT group, respectively (Figure 1). Further analysis showed that at 3 years follow-up, locoregional disease progression occurred less frequently in the nCRT group compared to the pCT group (19% vs. 37%, respectively; log-rank test p=0.024). No significant difference in the incidence of distant disease progression at 3 years was observed between the pCT and nCRT group (50% vs. 44%; log-rank test p=0.441), respectively.

TABLE 1. Comparison of baseline characteristics according to neoadjuvant treatment protocol, before and after propensity score matching

	Original cohort			**Propensity score matched cohort**		
Variables	**pCT (n=106)**	**nCRT (n=87)**	***p* value**	**pCT (n=86)**	**nCRT (n=86)**	***p* value**
Male gender*	87 (82.1)	77 (88.5)	0.214	73 (84.9)	76 (88.4)	0.502
Age (years)*	62.5 ± 8.8	64.6 ± 8.1	0.099	62.9 ± 8.9	64.5 ± 8.1	0.232
BMI (kg/m^2)*†	26.3 ± 3.8	26.3 ± 4.1	0.873	26.4 ± 3.9	26.2 ± 4.1	0.744
ASA score*			0.183			0.445
I	30 (28.3)	16 (18.4)		21 (24.4)	16 (18.6)	
II	68 (64.2)	60 (69.0)		58 (67.4)	59 (68.6)	
III	8 (7.5)	11 (12.6)		7 (8.1)	11 (12.8)	
WHO performance status*			0.086			0.169
0	57 (53.8)	36 (41.4)		45 (52.3)	36 (41.9)	
1	49 (46.2)	51 (58.6)		41 (47.7)	50 (58.1)	
COPD	11 (10.4)	10 (11.5)	0.804	8 (9.3)	10 (11.6)	0.618
Cardiac co-morbidity	25 (23.6)	30 (34.5)	0.095	20 (23.3)	30 (34.9)	0.093
Diabetes mellitus	11 (10.4)	13 (14.9)	0.339	10 (11.6)	13 (15.1)	0.502
History of smoking*	59 (55.7)	60 (69.0)	0.059	47 (54.7)	59 (68.6)	0.060
Surgical approach*			0.035			0.485
Transhiatal	23 (21.7)	9 (10.3)		12 (14.0)	9 (10.5)	
Transthoracic	83 (78.3)	76 (89.7)		74 (86.0)	77 (89.5)	
Tumor length on endoscopy (cm)†	5.3 ± 2.5	4.8 ± 2.3	0.219	5.3 ± 2.6	4.8 ± 2.3	0.191
Clinical T-stage*ǂ			0.301			0.514
T1	2 (1.9)	2 (2.3)		1 (1.2)	2 (2.3)	
T2	9 (8.5)	15 (17.2)		9 (10.5)	15 (17.4)	
T3	91 (85.8)	68 (78.2)		73 (84.9)	67 (77.9)	
T4	4 (3.8)	2 (2.3)		3 (3.5)	2 (2.3)	
Clinical N-stage*§			0.323			0.866
N0	25 (23.6)	26 (29.9)		24 (27.9)	25 (29.1)	
N+	81 (76.4)	61 (70.1)		62 (72.1)	61 (70.9)	

Note. Data are numbers of patients with percentages in parentheses.*Variables used for propensity matching. †Data are mean ± standard deviation. ǂClinical tumor stage (cT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[24]. §Clinical lymph-node (cN) stage classified according to the 7th edition of the UICC TNM classification[24]. BMI: Body Mass Index. ASA: American Society of Anesthesiologists. WHO: World Health Organization. COPD: Chronic Obstructive Pulmonary Disease.

TABLE 2. Comparative analysis of toxicity (grade 3 or higher) during neoadjuvant treatment*

Toxicity criteria	**pCT (n=86)**	**nCRT (n=86)**	***p* value**
Thromboembolic event (grade ≥3)	16 (18.6)	0 (0.0)	<0.001
Neutropenia (grade ≥3)	2 (2.3)	7 (8.1)	0.168
Febrile neutropenia (grade ≥3)	5 (5.8)	2 (2.3)	0.443
Leukopenia (grade ≥3)	3 (3.5)	12 (14.0)	0.015
Thrombocytopenia (grade ≥3)	1 (1.2)	5 (5.8)	0.210
Anemia (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Nausea (grade ≥3)	7 (8.1)	5 (5.8)	0.549
Vomiting (grade ≥3)	8 (9.3)	3 (3.5)	0.119
Diarrhea (grade ≥3)	7 (8.1)	0 (0.0)	0.014
Dehydration (grade ≥3)	2 (2.3)	3 (3.5)	0.650
Anorexia (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Esophageal perforation (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Gastric hemorrhage (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Dyspnea (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Allergic reaction (grade ≥3)	1 (1.2)	1 (1.2)	1.000
Acute coronary syndrome (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Any adverse event (grade ≥3)	39 (45.3)	34 (39.8)	0.440
Premature discontinuation	20 (23.3)	23 (26.7)	0.597
Post-operative continuation	34 (39.5)	NA	NA

Note. Data are numbers of patients with percentages in parentheses.*Adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0[21]

TABLE 3. Comparative analysis of postoperative course*

Outcome measure	**pCT (n=84)**	**nCRT (n=84)**	***p* value**
Complicated postoperative course	58 (69.0)	61 (72.6)	0.661
Anastomotic leakage[†]	20 (23.8)	24 (28.6)	0.483
Pneumonia[ǂ]	29 (34.5)	29 (34.5)	1.000
Cardiac arrhythmia[§]	11 (12.6)	20 (23.8)	0.058
Chyle leak[‖]	14 (16.7)	12 (14.3)	0.870
Recurrent nerve paresis	6 (7.1)	8 (9.5)	0.577
Wound infection	3 (3.6)	5 (6.0)	0.469
Postoperative bleeding	2 (1.2)	2 (2.4)	1.000
Thromboembolic event	5 (6.0)	5 (6.0)	1.000
Clavien-Dindo grade[¶]			0.334
I	7 (8.3)	8 (9.5)	
II	28 (33.3)	19 (22.6)	
IIIa	0 (0.0)	3 (3.6)	
IIIb	6 (7.1)	14 (16.7)	
IV	15 (17.9)	11 (13.1)	
V	3 (3.6)	6 (7.1)	
Grade IIIb or higher	23 (27.4)	31 (36.9)	0.186
Duration of hospital stay (days)[#]	15 [11-23]	16 [11-27]	0.465
Duration of ICU stay (days)[#]	1 [1-4]	1 [1-4]	0.563
30-day mortality	1 (1.2)	2 (2.4)	1.000
90-day mortality	5 (6.0)	6 (7.1)	0.755

Note. Data are numbers of patients with percentages in parentheses.*Of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively. [†]Anastomotic leakage included all clinical and radiological findings of anastomotic dehiscence or fistula. [ǂ]Pneumonia was defined by the universal pneumonia score[40]. [§]Cardiac arrhythmia were defined as any change in rhythm on an electrocardiogram requiring treatment. [‖]Chyle leak was defined as elevated levels of triglycerides in intrathoracic fluid requiring treatment. [¶]Clavien-Dindo classification, a surgical complication grading system[22,23]. [#]Data presented as median with interquartile range [IQR] between brackets.

TABLE 4. Comparative analysis of postoperative histopathology*

Outcome	pCT (n=84)	nCRT (n=84)	*p* value
Pathologic T-stage†	9 (10.7)	15 (17.9)	0.131
ypT0	12 (14.3)	10 (11.9)	
ypT1b	12 (14.3)	19 (22.6)	
ypT2	48 (57.1)	38 (45.2)	
ypT3	3 (3.6)	2 (2.4)	
ypT4			
Pathologic N-stage‡	36 (42.9)	42 (50.0)	0.353
ypN0	48 (57.1)	42 (50.0)	
ypN1			
Tumor regression grade§	9 (10.7)	15 (17.9)	<0.001
I	5 (6.0)	16 (19.0)	
II	17 (20.2)	27 (32.1)	
III	18 (21.4)	22 (26.2)	
IV	35 (41.7)	4 (4.8)	
V			
Radicality of resection‖	75 (89.3)	80 (95.2)	0.149
R0	9 (10.7)	4 (4.8)	
R1			

Note. Data are numbers of patients with percentages in parentheses. *Of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively. †Pathological tumor stage (pT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[24]. ‡Pathological lymph-node (pN) stage classified according to the 7th edition of the UICC TNM classification[24]. The (circumferential) resection margin was evaluated using the College of American Pathologist (CAP) criteria. §Histopathologic tumor regression graded according to the system proposed by Mandard et al.[26] ‖The (circumferential) resection margin was evaluated using the College of American Pathologist criteria[25]

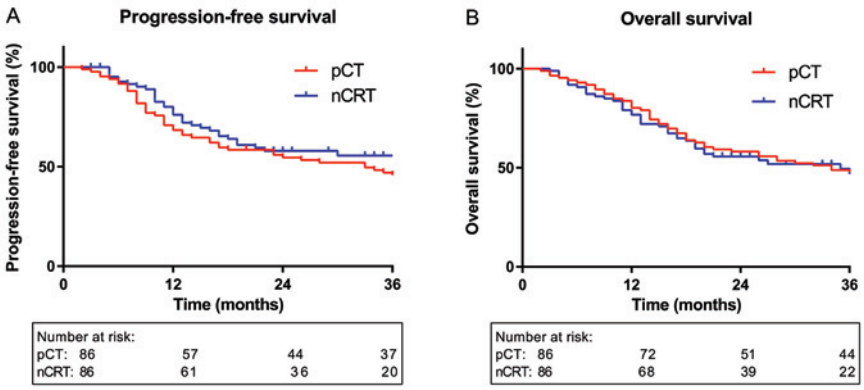

Figure 1. Comparison of progression-free survival (A) and overall survival (B) in propensity score-matched perioperative chemotherapy and neoadjuvant chemoradiotherapy followed by esophagectomy groups.

DISCUSSION

In this propensity score-matched cohort study, outcomes of perioperative chemotherapy were compared to neoadjuvant chemoradiotherapy for patients with resectable esophageal or GEJ adenocarcinoma. No significant improvements were achieved with nCRT as compared to pCT in terms of radical resection rates or progression-free survival and overall survival. However, nCRT was associated with improved tumor downstaging and a higher pathCR rate compared to chemotherapy. This observation likely translated into the observed decrease in locoregional disease progression in the nCRT group.

According to recent literature, pCT and nCRT both improve survival compared to surgery alone in patients treated for esophageal or GEJ adenocarcinoma[4,6]. In two meta-analyses, indirect treatment comparisons have suggested a greater survival benefit of nCRT over pCT[5,7]. However, in both meta-analyses the difference between the two groups did not reach statistical significance. This finding corresponds with the direct comparison in our study that showed no significant survival benefit for one of the regimens.

Until now, three randomized trials have made a similar attempt to directly compare nCRT with pCT for patients with esophageal or GEJ adenocarcinoma[28-30]. Stahl et al., randomly allocated 119 patients to either chemotherapy (cisplatin, 5-FU, leucovorin) or chemoradiotherapy (cisplatin, 5-FU, leucovorin, 30 and Gy) both followed by surgery[28]. The chemoradiotherapy arm showed a higher probability of pathologic complete response (2% after chemotherapy vs. 16% after nCRT, p=0.03) and a reduction in locoregional recurrence (41% after chemotherapy vs. 23% after nCRT; p=0.06). Although the study was closed early due to slow patient accrual, there was a trend towards a 3-year overall survival advantage (28% vs. 48%, p=0.07) for the nCRT group. In a comparable trial by Burmeister et al., 75 patients were randomized to receive either preoperative chemotherapy (cisplatin, 5-FU) or preoperative chemoradiotherapy (cisplatin, 5-FU, and 35 Gy)[29]. This study showed a higher histopathological complete response (13% vs. 0%) and R0 resection rate (100% vs. 89%) for patients treated with chemoradiotherapy compared to chemotherapy, respectively but no difference in survival was observed[29]. A recent randomized controlled trial of 181 patients by Klevebro et al., again showed a higher pathCR rate (28% vs. 9%; p=0.002) in patients treated with nCRT (platin, 5-FU, and 40 Gy) compared to neoadjuvant chemotherapy (platin, 5-FU), with comparable survival between the two groups[30].

Our finding that nCRT increases the pathCR rate corresponds with the studies discussed above. The nCRT group yielded a 18% pathCR rate compared to 11% in the pCT group ($p<0.001$),

respectively. Additionally, in the current series a significantly lower incidence of locoregional tumor progression and a trend towards a higher R0 resection rate was found after nCRT. This supports the theory of effective tumor downstaging in this group. Pathologic response after neoadjuvant treatment is a major determinant of survival in patients with esophageal cancer[8,26,31-33]. Interestingly, in the current study and in the mentioned comparative studies, increased pathCR rates and improved local control did not translate into a significant survival benefit for the nCRT group. However, given that the majority of patients undergoing either nCRT or pCT will have distant disease progression, there is need for feasible (adjuvant) treatments that result in effective systemic tumor elimination of micrometastases. As local control after nCRT is reasonable, currently the interest in adjuvant chemotherapy in these patients to increase systemic control is increasing. A recent cohort study has shown that this approach may improve survival in patients with residual nodal disease[34]. Future trials are underway and should answer whether the addition of new adjuvant therapies will improve survival by reducing distant disease progression[35,36].

In addition to improving oncologic results, objective evaluation of the risk and benefits must be considered when comparing different types of neoadjuvant therapy. One of the well-established limitations of perioperative chemotherapy regimens is that adjuvant chemotherapy is less feasible than preoperative chemotherapy[4,13,37]. In the MAGIC and FNCLCC/FFCD trials, for example, the proportion of patients who received postoperative chemotherapy was 55% and 48%, respectively[4,13]. Also in the current study a limited number of patients initiated postoperative chemotherapy (40%). However, despite the fact that compliance with postoperative chemotherapy is often limited, a clear survival benefit of perioperative chemotherapy over surgery alone has been well established[4,13]. The role of postoperative chemotherapy may be debated, as a recent meta-analysis showed no difference in survival between treatment with perioperative chemotherapy and preoperative chemotherapy only[38]. The feasibility problems of the currently available perioperative chemotherapy regimens favor the use of neoadjuvant treatment.

Another disadvantage of neoadjuvant therapies is the associated toxicity, which could contribute to an increase in postoperative morbidity and mortality[39]. In the current study, both treatment strategies caused substantial regimen-specific toxicity that are comparable with earlier reports[10,15,17]. Also, no significant difference with regard to severity and incidence of postoperative morbidity or perioperative mortality between the pCT and nCRT groups were observed. These results are consistent with two recent meta-analyses that compared postoperative morbidity and mortality between patients treated with pCT or nCRT for

esophageal (adeno)carcinoma and found no differences[40,41]. On the other hand, in a recent randomized controlled trial more severe postoperative complications were observed after nCRT compared to chemotherapy[42].

The anastomotic leak rates of 24-29% in the current series were substantially higher compared to other studies[40,43,44]. However, our definition of anastomotic leakage was rather un-restricted including any sign of clinical, endoscopic or radiological prove of anastomotic leakage. As such, the leakage rate in this study appears to be comparable with the leakage rates of 22% to 30% that were presented in the recent CROSS-trial[10].

Strengths of this study include the use of predominantly prospective collected data. Furthermore, the sample size of this study is relatively large compared to previous comparative studies. Lastly, this is one of the first studies that directly compares two highly recommended multimodality treatment regimens (ECC vs. CROSS) for patients with esophageal or GEJ adenocarcinoma. Potential limitations of this study include its retrospective character and lack of randomization. In order to adjust for the potentially resulting confounding bias, propensity score matching was performed to improve the comparability of the two groups. However, the inability of propensity score matching to adjust for unknown confounders that could explain some of our findings remains a limitation. Due to the inclusion of two groups receiving treatment in different time periods it is possible that unknown confounders have changed over time which to some extent might have created differences between the two groups. Survival, for example, could have been influenced by developments in available therapies for treatment of esophageal adenocarcinoma upon recurrence. Recent studies have demonstrated that treatment with ramucirumab monotherapy and ramucirumab combined with paclitaxel improves survival compared to placebo in patients with recurrent GEJ adenocarcinoma[45,46]. Therefore, treatment of recurrent disease may not have been the same throughout the whole study period, which may have improved the prognosis of the nCRT patients that were included later in this study. Also, the addition of a diagnostic ^{18}F-FDG PET/CT as part of initial staging in more recent years may to some extent have improved the prognosis of these patients, through improved patient selection for treatment with curative intent. Furthermore, the median-follow up in the nCRT group was relatively short. Therefore, subtle effects on progression-free survival and overall survival cannot be excluded. Currently, several randomized trials comparing chemotherapy and nCRT regimens are underway and should resolve the limitations in the current literature (CROSS versus MAGIC [NCT01726452], NEOSCOPE-trial [NCT01843829][47], TOPGEAR-trial [NCT01924819][48]).

In conclusion, perioperative chemotherapy and neoadjuvant chemoradiotherapy are both associated with substantial regimen-specific adverse events and postoperative morbidity. Neoadjuvant chemoradiotherapy achieves higher pathologic complete response rates and a lower risk of locoregional disease progression, with similar survival compared to perioperative chemotherapy.

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17

Neoadjuvant radiation to the gastric fundus increases the risk of anastomotic leakage after transthoracic esophagectomy for esophageal cancer

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ABSTRACT

Objective

Concerns have been raised regarding the toxicity of neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer that could contribute to an increased risk of postoperative complications. The aim of this study was to determine the influence of the radiation dose to the gastric fundus on the risk of postoperative anastomotic leakage in patients undergoing nCRT followed by transthoracic esophagectomy.

Methods

Between January 2012 and July 2015, 97 consecutive patients who underwent nCRT followed by transthoracic esophagectomy were included in this single-center cohort study. The gastric fundus was contoured on the pre-treatment planning CT. Within this contour, dose-volume histogram parameters were calculated and logistic regression analysis was used to determine their influence on the risk of anastomotic leakage

Results

In 25 (26%) of 97 patients anastomotic leakage occurred. The mean radiation dose to the gastric fundus was significantly higher in patients with versus without leakage (median 35.6Gy versus 24.9Gy, respectively; p=0.047). A mean dose above versus below 31.4 Gy was associated with leakage rates of 43% versus 15%, respectively. Adjusted for tumor location, clinical T-stage, and radiation modality, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted odds ratio 1.05 per 1Gy increase, 95% confidence interval: 1.002-1.10; p=0.043).

Conclusion

Efforts should be made to minimize the radiation dose to the gastric fundus when planning nCRT for esophageal cancer, since higher dose levels to the gastric fundus are associated with an increased risk of anastomotic leakage after subsequent transthoracic esophagectomy and cervical anastomosis.

INTRODUCTION

Esophagectomy is the cornerstone of curative treatment for esophageal cancer and the long-term survival benefit of neoadjuvant chemoradiotherapy (nCRT) is well established[1-3]. Over the past decades, a steady decrease in postoperative mortality has been achieved by improvements of surgical techniques and perioperative management[4]. However, anastomotic leakage of the esophagogastrostomy remains one of the major complications negatively impacting surgical and oncologic outcomes[4,5]. Reported incidence rates of anastomotic leakage after esophagectomy range between 6% and 41%[2, 6-10].

Concerns have been raised regarding the toxicity of nCRT that could contribute to an increased risk of postoperative complications. Several non-randomized studies reported an increase in surgical morbidity in patients that underwent nCRT[11-14]. Postoperative pulmonary complications have convincingly been related to neoadjuvant radiation dose to the lungs[15-17]. However, the influence of neoadjuvant radiation on postoperative anastomotic leakage has been less extensively studied. In this respect, radiation dose to the gastric fundus is of interest as this part of the stomach is used for the esophagogastric anastomosis.

The available evidence on the potential association between neoadjuvant radiation dose to the gastric fundus and the risk of anastomotic leakage after esophagectomy is equivocal[18,19]. Therefore, currently it remains unclear whether efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation treatment for esophageal cancer. The aim of the present study was to determine the influence of neoadjuvant radiation dose to the gastric fundus on the risk of anastomotic leakage in a large homogeneous cohort of patients with esophageal cancer undergoing nCRT followed by transthoracic esophagectomy and cervical anastomosis.

METHODS

Study population

This study was approved by our institutional review board, and the informed consent requirement was waived. From a prospectively acquired database, consecutive patients with esophageal or gastro-esophageal junction (GEJ) cancer were identified who underwent nCRT followed by transthoracic esophagectomy between January 2012 and July 2015 at our tertiary referral center. All patients had biopsy-proven resectable carcinoma with no evidence of distant metastases. Patients who underwent transhiatal esophagectomy, salvage esophagectomy or non-elective surgery and patients in whom no gastric conduit reconstruction was performed were excluded.

Treatment protocol

The nCRT regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks combined with weekly intravenous administration of carboplatin/paclitaxel[2]. Some patients (with a clinical T4b tumor) received a total radiation dose of 50.4 Gy in 28 fractions of 1.8 Gy in 6 weeks. The gross tumor volume (GTV) was defined by the primary tumor and any suspicious regional lymph nodes as determined by all available information (endoscopy, EUS, CT, and ^{18}F-FDG PET if available). The clinical target volume (CTV) included the GTV plus a cranial and caudal margin of 3 cm; in case of tumor extension into the stomach a caudal margin of 2 cm was chosen. In addition, the CTV included a radial margin around the GTV of 0.5 cm, adjusted for anatomical structures. The planning target volume (PTV) was defined as the CTV plus a margin of 1 cm in all directions. Patients were treated by either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT).

Surgical treatment consisted of a transthoracic esophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction. A linear stapler (GIA™ 80, 3.8 mm, Covidien, Mansfield, MA, USA) was used to create a gastric conduit 4 cm wide, and the gastric conduit staple line was oversewn by hand. A cervical esophagogastric anastomosis was performed end-to-side with hand-sewn continuous sutures (3-0 PDS) in monolayer. The surplus of the gastric conduit was removed with a stapling device (GIA™ 80, 3.8 mm, Covidien, Mansfield, MA, USA) in all patients.

Data collection

Clinical patient characteristics, treatment details, and surgical outcome data were collected from the prospectively acquired database. Anastomotic leakage was defined as postoperative demonstration of saliva through the cervical wound, extravasation of water-soluble contrast during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical re-intervention[8].

Image analysis

The gastric fundus was retrospectively contoured on the pre-treatment planning CT (section thickness: 3.0 mm) using Volumetool software[20]. After consultation with the authors of a previous study[18], the boundaries of the delineated gastric fundus were standardized in accordance with the applied method in that study: the most proximal part of the stomach located within the diaphragmatic dome was determined in the transverse plane. From that point, four consecutive transverse sections in caudal direction were delineated following the boundaries of the stomach at these levels. The resulting region of interest (ROI) in

three dimensions was defined as the gastric fundus. The following dose-volume histogram parameters were calculated from the ROI: volume, mean dose, minimum dose, D50 (i.e. dose that covered at least 50% of the volume), maximum dose, V20, V25, V30, and V35 (i.e. percentage of the volume that received at least 20, 25, 30, and 35 Gy, respectively).

Statistical analysis

The association of baseline characteristics with anastomotic leakage was studied univariably. The Chi-square test (or Fisher's exact test in case of small cell counts) was used to compare categorical parameters, whereas the Student's T-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous parameters, respectively. Univariable logistic regression models were used to analyze whether the different radiation dose and volume characteristics of the gastric fundus influenced the risk of anastomotic leakage. For the radiation dose parameters that were significantly related to anastomotic leakage, receiver operating characteristics (ROC) analysis was performed to identify ideal cut-off values in which equal weight was given to sensitivity and specificity.

Three baseline characteristics including tumor location, clinical T-stage and radiation modality, were thought to potentially confound the association between radiation dose to the gastric fundus and anastomotic leakage, by potentially influencing both predictor (radiation dose) and outcome (anastomotic leakage). Therefore, the (mean) radiation dose to the gastric fundus was entered in a multivariable logistic regression model together with the three potential confounders to study the independent influences on the risk of anastomotic leakage. High correlations between some parameters were expected (e.g. V20-V35 values and mean dose), resulting in the statistical problem of (multi)collinearity. Therefore, from these highly correlated pairs of parameters only the mean dose was pre-selected for the multivariable model. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). A p-value of <0.05 was considered statistically significant.

RESULTS

In the study period a total of 115 patients with esophageal cancer were treated with nCRT followed by transthoracic esophagectomy. Of these patients, 18 were excluded because they received radiotherapy at another institution (n=15), the treatment planning CT did not include the level of the gastric fundus (n=1), the quality of the treatment planning CT was insufficient (n=1), or no surgical resection was performed due to unsuspected metastatic disease (n=1).

Among the 97 included patients, 25 (26%) developed postoperative anastomotic leakage. Of the patients with anastomotic leakage, treatment consisted of opening of the cervical wound and nil-by-mouth in 4 patients (16%), endoscopic re-intervention (stent placement) in 7 patients (28%), and surgical re-intervention in 14 patients (56%). Postoperative in-hospital mortality occurred in 3 of 97 patients (3.1%), of which two suffered from anastomotic leakage. In 30 (31%) of 97 patients postoperative pneumonia was diagnosed. No significant difference in incidence of pneumonia among patients with or without anastomotic leakage was found (24% versus 33%, respectively: p=0.384*).* Baseline characteristics and their univariable association with anastomotic leakage are presented in Table 1. None of the studied baseline characteristics were significantly associated with the occurrence of postoperative anastomotic leakage.

A comparison of gastric fundus radiation dose characteristics for patients with versus without anastomotic leakage is demonstrated in Table 2. In univariable logistic regression analysis, the mean radiation dose to the gastric fundus was significantly higher in patients with anastomotic leakage compared to patients without anastomotic leakage (median [IQR]: 35.6 Gy [20.2-39.9] versus 24.9 Gy [11.9-35.1], respectively; p=0.047). Also, in patients with anastomotic leakage the minimum radiation dose to the gastric fundus was significantly higher compared to patients without leakage (15.1 Gy [11.9-26.1] versus 8.9 Gy [2.8-16.9]; p=0.006) (Figure 1a). In addition, univariable analysis showed that percentages of the gastric fundus volume receiving a minimal dose of 25, 30, and 35 Gy (i.e. V25, V30, V35, respectively) were significantly higher in patients with anastomotic leakage (Figure 1b). In 32 (33%) of 97 included patients the maximum dose given to the fundus was as high as the dose given to the tumor. The volume of the gastric fundus and other radiation dose characteristics were not significantly associated with anastomotic leakage. Two typical examples of dose distributions in relation to the gastric fundus in patients with and without anastomotic leakage are depicted in Figure 2.

Ideal cut-off values as determined by ROC analysis for the parameters that were significantly related to anastomotic leakage are presented in Table 3. For example, the mean dose to the gastric fundus above which the risk of anastomotic leakage increased significantly was determined at 31.4 Gy. Patients with a mean dose above versus below this threshold developed anastomotic leakage in 43% versus 15% of cases, respectively.

The mean gastric fundus radiation dose given to proximal, middle, distal or gastro-esophageal junction tumors were 0.95 Gy ± 1.5, 15.6 Gy ± 13.9, 28.9 Gy ± 10.7, and 34.4 Gy ± 6.7 respectively. In multivariable analysis, the association between the (mean) neoadjuvant radiation dose to the gastric fundus and postoperative anastomotic leakage appeared not

confounded by tumor location, clinical T-stage or radiation modality (Table 4). Adjusted for these factors, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted odds ratio [OR] 1.05 per 1 Gy increase, 95% confidence interval [CI]: 1.002-1.10, p=0.043).

TABLE 1. Baseline characteristics

Characteristic	Anastomotic leakage (n = 25)	No anastomotic leakage (n = 72)	*p* value
Male gender	19 (76.0)	53 (73.6)	0.814
Age (years)*	64.9 ± 7.6	66.3 ± 7.3	0.414
BMI (kg/m^2)*	25.6 ± 4.6	25.5 ± 4.7	0.947
ASA score			0.262
I	5 (20.0)	14 (19.4)	
II	12 (48.0)	48 (66.7)	
III	8 (32.0)	10 (13.9)	
COPD	6 (24.0)	9 (12.5)	0.203
Cardiac co-morbidity	7 (28.0)	25 (34.7)	0.538
Vascular co-morbidity	12 (48.0)	33 (45.8)	0.852
Diabetes mellitus	4 (16.0)	10 (13.9)	0.751
History of smoking	17 (68.0)	52 (72.2)	0.688
Clinical T-stage			0.104
cT1	0 (0.0)	1 (1.4)	
cT2	3 (12.0)	19 (26.4)	
cT3	19 (76.0)	47 (65.3)	
cT4	3 (12.0)	5 (6.9)	
Clinical N-stage			0.529
cN0	5 (20.0)	19 (26.4)	
cN1	12 (48.0)	34 (47.2)	
cN2	7 (28.0)	15 (20.8)	
cN3	1 (4.0)	4 (5.6)	
Tumor histology			0.799
Adenocarcinoma	17 (68.0)	43 (59.7)	
Squamous cell carcinoma	8 (32.0)	27 (37.5)	
Other	0 (0.0)	2 (2.8)	
Tumor location			0.629
Proximal third of esophagus	2 (8.0)	6 (8.3)	
Middle third of esophagus	5 (20.0)	18 (25.0)	
Distal third of esophagus	15 (60.0)	41 (56.9)	
Gastro-esophageal junction	3 (12.0)	7 (9.7)	
Radiation modality			0.339
3D-CRT	11 (44.0)	24 (33.3)	
IMRT	14 (56.0)	48 (66.7)	
Radiation planning modality			0.576
CT	7 (28.0)	19 (26.4)	
^{18}FDG-PET/CT	18 (72.0)	53 (73.6)	
Total radiation dose			1.000
41.4 Gy (23 x 1.8 Gy)	23 (92.0)	67 (93.1)	
50.4 Gy (28 x 1.8 Gy)	2 (8.0)	5 (6.9)	
Intraoperative blood loss (mL)*	500 ± 295	502 ± 336	0.985

Note. Data are numbers of patients with percentages in parentheses.*Data are mean ± standard deviation.3D-CRT: three-dimensional conformal radiotherapy. IMRT: intensity-modulated radiotherapy.

TABLE 2. Univariable logistic regression analysis of gastric fundus dose characteristics among patients with versus without anastomotic leakage

Characteristic	Anastomotic leakage (n = 25)	No anastomotic leakage (n = 72)	OR (95% CI)	*p* value
Volume (mL)	11.1 [8.1-12.8]	11.8 [8.3-15.9]	0.92 (0.83-1.02)	0.121
Mean dose (Gy)	35.6 [20.2-39.9]	24.9 [11.9-35.1]	1.04 (1.00-1.08)	0.047
Minimum dose (Gy)	15.1 [11.9-26.1]	8.9 [2.8-16.9]	1.06 (1.02-1.11)	0.006
D50 (Gy)	39.0 [16.7-41.2]	21.8 [11.7-38.9]	1.03 (1.00-1.07)	0.054
Maximum dose (Gy)	42.5 [40.9-43.0]	41.9 [23.2-42.7]	1.02 (0.98-1.05)	0.328
V20 (%)	94.5 [27.5-100]	60.0 [2.6-93.9]	1.12 (0.99-1.27)†	0.066
V25 (%)	90.1 [22.3-99.8]	38.3 [0.0-81.3]	1.15 (1.02-1.30)†	0.025
V30 (%)	73.1 [17.9-96.1]	26.2 [0.0-76.5]	1.16 (1.02-1.31)†	0.021
V35 (%)	63.4 [13.2-93.3]	17.4 [0.0-65.2]	1.16 (1.03-1.32)†	0.018

Data presented as median with interquartile range (IQR) between brackets. †Odds ratio per 10% increase in volume-percentage.

TABLE 3. Receiver operating characteristics analysis of gastric fundus dose characteristics among patients with versus without anastomotic leakage

Characteristic	AUC	Ideal cut-off	SE (%)	SP (%)	PPV (%)	NPV (%)
Mean dose	0.66	31.4 Gy	64.0	70.8	43.2	85.0
Minimum dose	0.65	10.9 Gy	84.0	54.2	38.9	90.7
V25	0.65	89.7%	52.0	80.6	48.1	82.9
V30	0.65	59.3%	60.0	70.8	41.7	83.6
V35	0.65	54.7%	60.0	72.2	42.9	83.9

SE: sensitivity. SP: specificity. PPV: positive predictive value. NPV: negative predictive value.

TABLE 4. Results of multivariable logistic regression analysis with anastomotic leakage as outcome parameter

Characteristic	OR (95% CI)	*p* value
Tumor location		
Proximal or middle third of esophagus	1.00 (ref)	
Distal third of esophagus or GEJ	0.60 (0.16-2.17)	0.432
Clinical T-stage		
cT1-2	1.00 (ref)	
cT3-4	2.81 (0.73-10.77)	0.132
Radiation modality		
3D-CRT	1.00 (ref)	
IMRT	0.65 (0.25-1.74)	0.398
Mean radiation dose to gastric fundus	1.05 (1.002-1.10)	0.043

GEJ: gastro-esophageal junction. 3D-CRT: three-dimensional conformal radiotherapy. IMRT: intensity-modulated radiotherapy.

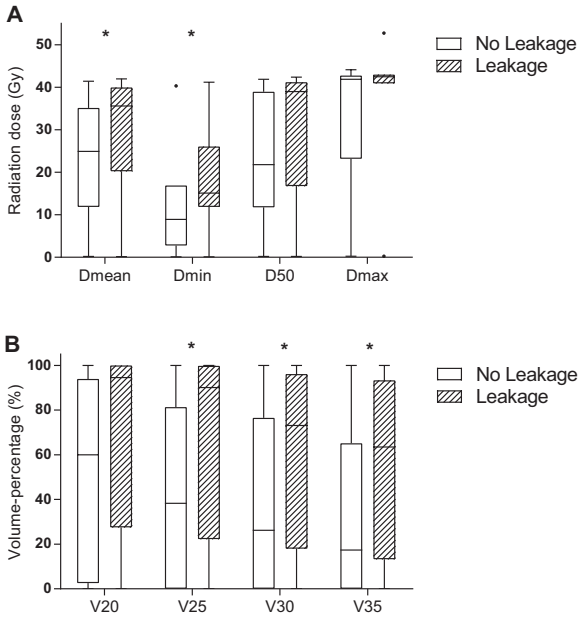

Figure 1. Box plots showing (A) the distribution of gastric fundus dose parameters (Dmean, Dmin, D50, Dmax), and (B) the distribution of gastric fundus volume percentages receiving a minimum amount of Gy (V20, V25, V30, V35) between patients with and without anastomotic leakage. The asterisk (*) indicates parameters significantly associated with anastomotic leakage.

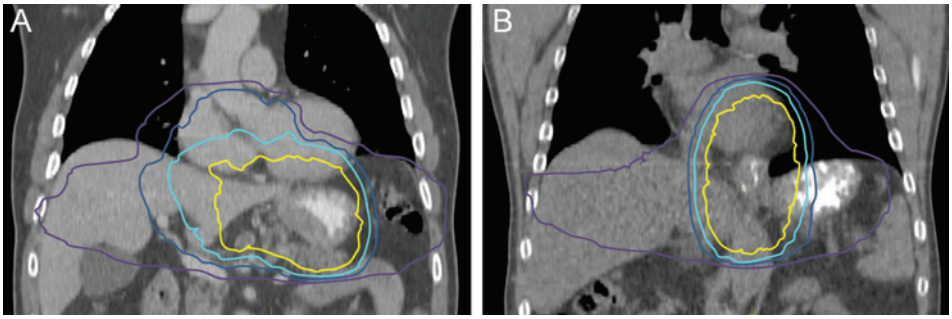

Figure 2. Examples of treatment planning CT scans with dose distributions in (A) a patient who developed postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 41.2 Gy, and in (B) a patient who did not experience postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 11.8 Gy. The areas within the yellow, light blue, dark blue and purple lines received at least 40, 30, 20, and 10 Gy, respectively.

DISCUSSION

This study demonstrates that the neoadjuvant radiation dose to the gastric fundus in patients with esophageal cancer has a significant impact on the risk of anastomotic leakage after transthoracic esophagectomy with cervical anastomosis. Several radiation dose characteristics appeared to be significant predictors of anastomotic leakage, including the mean and minimum dose, V25, V30, and V35. These findings suggest that efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation for esophageal cancer with planned transthoracic esophagectomy. Overall, 26% of patients developed anastomotic leakage in this series. According to the results of this study, limiting the mean dose to 31 Gy could decrease the risk of anastomotic leakage to 15% in this setting.

Two previous studies have reported on the relationship between neoadjuvant radiation dose to the gastric fundus and the risk of postoperative anastomotic leakage[18,19]. Similar to the current series, one study that included 54 patients treated with nCRT followed by Ivor-Lewis esophagectomy with intrathoracic anastomosis reported that the radiation dose to the gastric fundus was significantly related to the risk of anastomotic leakage[18]. However, in that study a different neoadjuvant treatment regimen (36 Gy in 20 fractions combined with 5-FU and cisplatin) and surgical procedure (Ivor-Lewis esophagectomy with intrathoracic anastomosis) were applied[18]. Of note, neoadjuvant treatment according to the CROSS-regimen as applied in the present study is currently regarded as the standard of care in many countries worldwide for patients with resectable locally advanced esophageal cancer[3].

In contrast, another recent study with 53 patients that underwent nCRT followed by transhiatal esophagectomy with cervical anastomosis found no influence of radiation dose to the gastric fundus on the occurrence of anastomotic leakage[19]. That study applied a similar neoadjuvant treatment regimen to the current series, but the surgical procedure (transhiatal esophagectomy with cervical anastomosis) was different[19]. However, transthoracic esophagectomy with en-bloc radical lymphadenectomy as was performed in the present study is currently considered the preferred approach of oncological esophagectomy[21,22]. Therefore, in contrast to other studies, the association between radiation dose to the gastric fundus and anastomotic leakage was analyzed under the circumstances of present-day standardized radical surgery and standardized neoadjuvant chemoradiotherapy in the current study. In addition, sample sizes across the two previous reports[18,19]. were small with only few events of anastomotic leakage (n=7 and n=13, respectively), which resulted in a substantial uncertainty of estimates and conclusions. This may be the reason for the more nuanced discriminatory ability of the mean dose to the gastric fundus to differentiate between patients with versus without leakage found

in the current series (i.e. area under the ROC curve [AUC] 0.66; Table 3) compared to those found in the other two studies (AUC 0.77[18], and approximately 0.50[19]).

The current evidence concerning the influence of nCRT on postoperative anastomotic leakage rates remains equivocal. A recent meta-analysis including 11 randomized controlled trials (RCTs) comparing outcomes of patients undergoing nCRT followed by surgery with patients who undergo surgery alone found that nCRT did not seem to increase the risk of postoperative anastomotic leakage (pooled risk ratio 1.00, 95% CI 0.74-1.35; p=0.878)[10]. However, another recent meta-analysis including 12 RCTs reported that nCRT potentially increases the risk of surgical morbidity, but that surgical morbidity was inconsistently reported across trials which impeded direct comparisons[1]. A recent retrospective analysis of 686 patients reported that anastomotic leakage developed more frequently in 376 patients who received nCRT than in the remaining patients who underwent surgery alone (28% versus 17%, respectively; p<0.01) (14). The current study was not designed - and hence does not allow - to answer the question whether nCRT *per se* increases the risk of postoperative anastomotic leakage, but rather to determine whether the variability of radiation doses to the gastric fundus relates to the risk of leakage. In the current study the maximum radiation dose given to the fundus was not associated with anastomotic leakage, while the mean dose and V25, V30, and V35 were associated with leakage. These results indicate that a higher dose spread over a larger volume rather than a high absolute maximum dose is indicative for the risk of anastomotic leakage after esophagectomy.

The conflicting evidence in the literature on the influence of nCRT on the risk of postoperative anastomotic leakage may in part be explained by the various definitions that are used for leakage. In some studies, anastomotic leakage is defined as clinical or radiological evidence of anastomotic dehiscence, whereas other definitions include only clinical leakage or anastomotic leakage that requires re-intervention only. In the current study, anastomotic leakage was defined as any postoperative evidence of leakage (either clinically or radiologically confirmed, and either or not requiring re-intervention), explaining the relatively high incidence rate of 26% in this study compared with other series[6,7,9, 10]. However, the leakage rate in this study appears to be comparable to the leakage rates of 22% to 30% that were reported in the recent CROSS-trial[2] which used the same nCRT regimen as the current study. Also, in accordance with the CROSS-trial[2], the used definition for anastomotic leakage in this study included subclinical leakage diagnosed on radiologic examination or endoscopy without clinical signs.

Sparing of the gastric fundus in radiation treatment planning for esophageal cancer could be achieved in various ways. The most obvious method would be the use of IMRT as highly conformal radiation therapy technique providing greater target volume conformity, greater dose homogeneity, and an increased ability to control dose to adjacent normal structures including the gastric fundus if desired. To this regard, it could be helpful if the radiation oncologist together with the surgeon assesses the radiation treatment planning to define which part of the fundus will be used for the gastro-esophageal anastomosis. In addition, one could think of reducing the caudal CTV margin in distal esophageal and GEJ tumors in the neoadjuvant setting to spare the gastric fundus, as the microscopic spread beyond the gross tumor is likely dealt with by surgical resection. This suggestion is supported by the finding that an irradical resection after nCRT, which occurs in 8% of patients[2], mostly involves microscopically positive surgical margins at the lateral (circumferential) borders rather than the caudal border[23]. On the other hand, such a margin-reducing strategy may increase the amount of residual tumor after nCRT outside the radiation field, which has been shown to negatively impact survival[24]. Finally, assessment of radiation dose to the gastric fundus could aid in individualized risk estimation of anastomotic leakage after esophagectomy.

Certain limitations apply to this study. First, although the largest study in this field, the sample size was relatively small hindering a more extensive multivariable analysis. Second, this study is limited by the retrospective nature of the analysis, which impedes adjustment for all potential factors that could explain our findings. Third, the gastric fundus is susceptible to breathing-induced organ motion, which could have altered radiation dose calculations. Since no daily imaging information was available the authors were not able to compensate for organ motion of the stomach nor for day-to-day treatment variations. Finally, unlike in other studies[18,19] the authors decided not to exclude patients with proximal and middle esophageal tumors. However, this decision was made deliberately to increase the observed variability of gastric fundus doses across patients, which increases the statistical power and precision of the effect estimates. The potential confounding effect of the resulting heterogeneity on the studied association between radiation dose and anastomotic leakage was corrected for in multivariable analysis.

In conclusion, this study demonstrates that the neoadjuvant radiation dose to the gastric fundus is associated with the risk of postoperative anastomotic leakage in patients with esophageal cancer treated with neoadjuvant chemoradiotherapy followed by transthoracic esophagectomy and cervical anastomosis. This finding is important for clinical practice because it suggests that efforts should be made to minimize the radiation dose.

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Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after esophagectomy for cancer

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ABSTRACT

Objective

Studies comparing the anastomotic leak rate in patients with an intrathoracic *versus* a cervical anastomosis after esophagectomy are equivocal. The aim of this study was to compare clinical outcome after esophagectomy in patients with an intrathoracic or cervical anastomosis, and to identify predictors of anastomotic leakage in a nationwide audit.

Methods

Between January 2011 and December 2015, all consecutive patients who underwent esophagectomy for cancer were identified from the Dutch Upper Gastrointestinal Cancer Audit. For the comparison between an intrathoracic and cervical anastomosis, propensity score matching was used to adjust for potential confounders. Multivariable logistic regression modeling with backward stepwise selection was used to determine independent predictors of anastomotic leakage.

Results

Some 3348 patients were included. After propensity score matching, 654 patients were included in both the cervical and intrathoracic anastomosis groups. An intrathoracic anastomosis was associated with a lower leak rate than a cervical anastomosis (17.0 *versus* 21.9 per cent; $P = 0.025$). The percentage of patients with recurrent nerve paresis was also lower (0.6 *versus* 7.0 per cent; $P < 0.001$) and an intrathoracic anastomosis was associated with a shorter median hospital stay (12 *versus* 14 days; $P = 0.001$). Multivariable analysis revealed that ASA fitness grade III or higher, chronic obstructive pulmonary disease, cardiac arrhythmia, diabetes mellitus and proximal esophageal tumors were independent predictors of anastomotic leakage.

Conclusion

An intrathoracic esophagogastric anastomosis was associated with a lower anastomotic leak rate, lower rate of recurrent nerve paresis and a shorter hospital stay. Risk factors for anastomotic leak were co-morbidities and proximal tumors.

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality, and its incidence continues to increase every year[1]. According to international guidelines[2], esophagectomy is the cornerstone of curative treatment for non-metastasized esophageal cancer, often combined with neoadjuvant or perioperative chemo(radio)therapy. Improvement in surgical techniques, perioperative management and patient selection have resulted in a reduction in postoperative mortality after esophagectomy[3]. However, anastomotic leakage remains relatively common, and is a major cause of morbidity and mortality. The percentage of patients with anastomotic leakage varies from 6 to 41 per cent[4–8].

Several factors are associated with an increased risk of anastomotic leakage, including patient-related characteristics[5,9,10], intraoperative factors[11–13], postoperative factors and surgical technique[14–16]. Controversy remains about the optimal anatomical location of the esophagogastric anastomosis (intrathoracic *versus* cervical) after esophagectomy. Several retrospective studies and one RCT reported increased leak rates in patients with a cervical anastomosis[9,17,18]. Other studies, including three RCTs[19–21], did not show a statistically significant difference in leak rates. Some surgeons accept a possible higher leak rate associated with a cervical anastomosis, because a wider oncological resection margin can be achieved. Furthermore, in patients with an anastomotic leak, the sequela may be less severe for a cervical anastomosis than for an intrathoracic anastomosis[22]. Others advocate that an intrathoracic anastomosis is associated with a lower leak rate because the gastric tube is shorter and better vascularized[9].

The scientific evidence for an association between the location of the anastomosis and risk of anastomotic leakage, postoperative morbidity and positive oncological resection margins after esophagectomy is equivocal. Therefore, the primary aim of this study was to assess anastomotic leakage rates, postoperative morbidity and radical resection rates after esophageal resection with either an intrathoracic or cervical esophagogastric anastomosis. A secondary objective was to identify predictors of anastomotic leakage.

METHODS

All patient data were obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a registry of all patients undergoing surgery with curative intent for esophageal or gastric cancer in the Netherlands. The DUCA is a subdivision of the Dutch Institute for Clinical Auditing, founded in 2011, with the objective to facilitate and organize the initiation of nationwide auditing in a uniform format. The DUCA collects data to monitor national guideline adherence

and to provide surgical teams with reliable information on outcome measures. Participation is mandatory for all Dutch hospitals performing esophageal resections, and data are registered for each patient during the hospital stay and until 30 days after discharge. Detailed descriptions of definitions used in the DUCA are provided in an online registry program to stimulate uniform data registration. An independent monitoring team audits the data to evaluate completeness and concordance. The organization of the DUCA has been described in more detail previously[23].

Patients

All patients undergoing esophagectomy for esophageal cancer with gastric tube reconstruction between January 2011 and December 2015 were included. For the comparison between intrathoracic and cervical anastomoses, transhiatal resections were excluded because an intrathoracic anastomosis was never performed during this approach. All proximal tumors were also excluded because a cervical anastomosis is constructed in patients with a proximal tumor. To assess factors associated with anastomotic leakage, all patients were studied.

Treatment

Surgical treatment consisted of an open (both abdomen and chest), hybrid (abdomen minimally invasive and open chest) or totally minimally invasive transthoracic esophagectomy followed by gastric tube construction with a cervical or intrathoracic anastomosis. The location and technique of the anastomosis (stapled *versus* handsewn, end-to-side *versus* side-to-side) are not specified in the DUCA. Patients received neoadjuvant treatment according to national guidelines.

Outcome measures

Patient and treatment-related characteristics were extracted from the DUCA. Histopathological, surgical and short-term oncological outcomes were analyzed. Surgical outcome parameters included: clinical or radiological anastomotic leakage, pneumonia, recurrent nerve paresis, surgical reintervention under general anesthesia, duration of hospital stay, duration of ICU stay, mortality within 30 days after surgery and/or in-hospital death, readmissions within 30 days after discharge, positive resection margin and number of retrieved lymph nodes.

Statistical analysis

Patient and treatment-related characteristics are described as count with percentages, mean(s.d.) or median (range), as appropriate. Missing values were encountered in 217 patients for eight variables; the percentage of missing values per variable was limited (range 0.0 to 4.9 per variable). It was not possible to recover missing data because patient and hospital identity

are concealed in the DUCA. Missing data were considered at random and handled using imputation with the iterative Markov chain Monte Carlo method (5 iterations)[24].

To account for the effect of possible confounders on outcomes, propensity score matching was performed for the analysis of intrathoracic *versus* cervical anastomosis. First, propensity scores (the probability, ranging from 0 to 1, that a patient was assigned to an intrathoracic or cervical anastomosis) were derived using a logistic regression model, which included all patient and treatment-related characteristics presented in *Table 1*. One-to-one propensity score matching was performed with nearest-neighbor matching without replacement, using a caliper width of 0.25 multiplied by the standard deviation of the estimated propensity score[25]. Balance in measured patient and treatment-related characteristics of the matched cohort was assessed using standardized mean differences, with differences of less than 10 per cent and close to 0 per cent taken to indicate good balance[26]. To evaluate the significance of differences between the two treatment groups, the c^2 test was used for categorical variables, and the Student's *t* test and Mann–Whitney *U* test for continuous variables with a normal and skewed distribution respectively. Logistic regression analysis was used to stratify by type of surgery (open *versus* total minimally invasive approach) in the propensity-matched cohort by adding an interaction term between surgical approach and anastomotic location for each outcome. For this analysis, hybrid procedures were added to the minimally invasive group.

The potential association between preoperative patient characteristics and anastomotic leakage was evaluated using univariable analyses in all patients (also including proximal tumors and patients who underwent a transhiatal resections). Variables with $P < 0.250$ in univariable analysis were entered into a multivariable logistic regression model with backward stepwise selection to determine independent predictors of anastomotic leakage. Multivariable Poisson regression with log link and robust error variance of the final model was used to determine relative risk (RR) estimates with 95 per cent confidence intervals. Statistical analyses were undertaken using SPSS® version 23.0 (IBM, Armonk, New York, USA), and R 3.1.2 open-source software with MatchIt and optmatch, sandwich, lmtest and Mice packages (http://www.R-project.org). $P < 0.050$ was considered statistically significant.

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RESULTS

Of 3348 patients selected for the study, 2086 were included in the comparison between an intrathoracic anastomosis (928) and a cervical anastomosis (1158) (*Fig. 1*). Patients were predominantly men (77.4 per cent), and the mean age was 64.6 (s.d. 9.0) years. The percentage of patients with an intrathoracic anastomosis increased during the study interval from 20.6 per cent in 2011 to 59.3 per cent in 2015. Patient and treatment-related characteristics according to location of the anastomosis are shown in *Table 1*. After propensity matching, 654 patients

were included in both groups and all baseline variables including year of surgery were equally distributed (SMD less than 10 per cent).

Intrathoracic versus cervical anastomoses

Postoperative complications and pathological data are shown in *Table 2*. Anastomotic leakage was less frequent in patients who underwent an intrathoracic anastomosis than in those with a cervical anastomosis: 111 of 654 (17.0 per cent) *versus* 143 of 654 (21.9 per cent) respectively ($P = 0.025$). Recurrent nerve paresis occurred less often in patients with an intrathoracic anastomosis: 4 of 654 (0.6per cent) *versus* 46 of 654 (7.0 per cent) respectively ($P < 0.001$). The median duration of hospital stay was shorter in patients with an intrathoracic anastomosis: 12 (range 3–145) *versus* 14 (range 4–386) days ($P < 0.001$). Surgical reinterventions, duration of ICU stay, in-hospital mortality and number of readmissions were comparable between the two groups. The associations between location of the anastomosis and outcome parameters were not statistically significant when stratified by type of surgical approach (P for interaction > 0.050) (*Table 2*).

Among patients with an anastomotic leak, there was no significant difference between the anastomosis groups in the percentage of patients who had a surgical reintervention (53.2 per cent of patients with an intrathoracic anastomosis *versus* 44.8 per cent with a cervical anastomosis; $P = 0.184$) or in-hospital mortality (8.1 *versus* 10.5 per cent respectively; $P = 0.520$). Duration of hospital stay (median 40 (range 9–132) *versus* 28 (4–132) days; $P < 0.001$) and length of ICU stay (median 8 (1–111) *versus* 4 (1–155) days; $P = 0.021$) were longer after an intrathoracic compared with a cervical anastomotic leak.

Predictors of anastomotic leakage

Some 656 of 3348 patients (19.6 per cent) had an anastomotic leak (*Table 3*, *Fig. 1*). The median duration of hospital stay was 26 (range 3–200) days in patients with anastomotic leakage compared with 11 (1-386) days in patients without an anastomotic leak ($P < 0.001$). Mortality rates were 9.1 and 2.7 per cent respectively ($P = 0.001$).

Univariable analysis revealed that anastomotic leakage was associated with several patient related factors including age, ASA fitness grade, tumor location and co-morbidities (*Table 3*). Tumor histology, TNM stage and neoadjuvant therapy did not differ between the groups with or without an anastomotic leak.

Independent predictors of the development of anastomotic leakage included: an ASA grade of III (RR 1.31, 95 per cent c.i. 1.09 to 1.78; $P = 0.009$) or IV (RR 1.98, 1.27 to 3.64; $P = 0.026$), history of chronic obstructive pulmonary disease (COPD) (RR 1.21, 1.02 to 1.45; $P = 0.031$), history of cardiac arrhythmia (RR 1.25, 1.01 to 1.55, $P = 0.044$), diabetes mellitus (RR 1.26, 1.06 to 1.49; $P = 0.009$) and tumor of the proximal esophagus (RR 1.86, 1.25 to 2.77; $P = 0.022$) (*Table 4*).

TABLE 1. Patient and treatment-related characteristics according to location of the anastomosis, before and after propensity score matching

		Before matching (n = 2086)			After matching (n = 1308)		
		Intrathoracic anastomosis (n = 928)	Cervical anastomosis (n = 1158)	SMD(%)	Intrathoracic anastomosis (n = 654)	Cervical anastomosis (n = 654)	SMD(%)
Age (years)*		64.1(9.0)	63.9((8.6)	2.7	64.1(8.9)	64.0(8.3)	2.7
Sex	M	779 (83.9)	835 (72.1)	32.2	526 (80.4)	533 (81.5)	2.9
	F	149 (16.1)	323 (27.9)		128 (19.6)	121 (18.5)	
BMI (kg/m^2)*		26.2(4.2)	25.4 (4.2)	21.0	26.0(4.2)	26.2 (4.2)	1.2
ASA fitness grade	I	150 (16.2)	215 (18.6)	9.0	110 (16.8)	109 (16.7)	5.0
	II	571 (61.5)	726 (62.7)		423 (64.7)	408 (62.4)	
	III	207 (22.3)	212 (18.3)		121 (18.5)	134 (20.5)	
	IV	0 (0)	5 (0.4)		0 (0)	3 (0.5)	
COPD	No	807 (87.0)	1021 (88.2)	3.6	574 (87.8)	568 (86.9)	2.7
	Yes	121 (13.0)	137 (11.8)		80 (12.2)	86 (13.1)	
Coronary artery disease	No	830 (89.4)	1063 (91.8)	7.7	593 (90.7)	597 (91.3)	2.0
	Yes	98 (10.6)	95 (8.2)		61 (9.3)	57 (8.7)	
History of myocardial infarction	No	861 (92.8)	1102 (95.2)	9.2	616 (94.2)	614 (93.9)	1.2
	Yes	67 (7.2)	56 (4.8)		38 (5.8)	40 (6.1)	
History of arrhythmia	No	844 (90.9)	1072 (92.6)	5.7	598 (91.4)	598 (91.4)	0.0
	Yes	84 (9.1)	86 (7.4)		56 (8.6)	56 (8.6)	
Hypertension	No	643 (69.3)	793 (68.5)	1.8	449 (68.7)	449 (68.7)	0.0
	Yes	285 (30.7)	365 (31.5)		205 (31.3)	205 (31.3)	
Peripheral vascular disease	No	891 (96.0)	1126 (97.2)	6.3	634 (96.9)	634 (96.9)	0.0
	Yes	37 (4.0)	32 (2.8)		20 (3.1)	20 (3.1)	
Diabetes mellitus	No	780 (84.1)	1010 (87.2)	8.6	553 (84.6)	561 (85.8)	3.3
	Yes	148 (15.9)	148 (12.8)		101 (15.4)	93 (14.2)	
History of stroke	No	872 (94.0)	1102 (95.2)	5.0	618 (94.5)	615 (94.0)	1.9
	Yes	56 (6.0)	56 (4.8)		36 (5.5)	39 (6.0)	

Thromboembolic events	No	887 (95.6)	1120 (96.7)	5.5	632 (96.6)	631 (96.5)	0.7
	Yes	41 (4.4)	38 (3.3)		22 (3.4)	23 (3.5)	
Endocrine disorder	No	895 (96.4)	1113 (96.1)	1.8	630 (96.3)	628 (96.0)	1.7
	Yes	33 (3.6)	45 (3.9)		24 (3.7)	26 (4.0)	
Previous abdominal or thoracic surgery	No	657 (70.8)	822 (71.0)	0.4	470 (71.9)	475 (72.6)	1.7
	Yes	271 (29.2)	336 (29.0)		184 (28.1)	179 (27.4)	
Histology	ADC	814 (87.7)	723 (62.4)	77.0	545 (83.3)	533 (81.5)	5.6
	SCC	96 (10.3)	392 (33.9)		92 (14.1)	104 (15.9)	
	Other	18 (1.9)	43 (3.7)		17 (2.6)	17 (2.6)	
Tumor location†	Middle	42 (4.5)	319 (27.5)	110.7	42 (6.4)	47 (7.2)	3.7
	Distal	886 (95.5)	839 (72.5)		612 (93.6)	607 (92.8)	
cT category	T1	49 (5.3)	64 (5.5)	6.4	35 (5.4)	42 (6.4)	0.3
	T2	190 (20.5)	216 (18.7)		125 (19.1)	117 (17.9)	
	T3	665 (71.7)	819 (70.7)		474 (72.5)	470 (71.9)	
	T4	24 (2.6)	59 (5.1)		20 (3.1)	25 (3.8)	
cN category	N0	364 (39.2)	370 (32.0)	18.9	230 (35.2)	242 (37.0)	0.4
	N1	388 (41.8)	503 (43.4)		283 (43.3)	268 (41.0)	
	N2	156 (16.8)	238 (20.6)		125 (19.1)	117 (17.9)	
	N3	20 (2.2)	47 (4.1)		16 (2.4)	27 (4.1)	
Neoadjuvant therapy	No	79 (8.5)	95 (8.2)	0.4	50 (7.6)	54 (8.3)	1.3
	nCT	52 (5.6)	75 (6.5)		49 (7.5)	46 (7.0)	
	nCRT	797 (85.9)	988 (85.3)		555 (84.9)	554 (84.7)	
Type of surgery	Open	199 (21.4)	355 (30.7)	22.4	161 (24.6)	170 (26.0)	3.4
	MI	716 (77.2)	791 (68.3		487 (74.5)	479 (73.2)	
	Hybrid	13 (1.4)	12 (1.0)		6 (0.9)	5 (0.8)	

TABLE 1 (continued). Patient and treatment-related characteristics according to location of the anastomosis, before and after propensity score matching

		Before matching (n = 2086)			After matching (n = 1308)		
		Intrathoracic anastomosis (n = 928)	Cervical anastomosis (n = 1158)	SMD(%)	Intrathoracic anastomosis (n = 654)	Cervical anastomosis (n = 654)	SMD(%)
Year of surgery	2015	328 (35.3)	225 (19.4)	61.7	174 (26.6)	164 (25.1)	1.9
	2014	248 (26.7)	234 (20.2)		157 (24.0)	178 (27.2)	
	2013	190 (20.5)	212 (18.3)		164 (25.1)	135 (20.6)	
	2012	108 (11.6)	279 (24.1)		105 (16.1)	125 (19.1)	
	2011	54 (5.8)	208 (18.0)		54 (8.3)	52 (8.0)	

Values in parentheses are percentages unless indicated otherwise;*values are mean(s.d.). Patients with proximal tumors and those who underwent a transhiatal resection were excluded from the analysis. All variables presented in *Table 1* were used for propensity matching. †Middle indicates 24–32 cm from teeth, and distal more than 32 cm from teeth. SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy; MI, minimally invasive.

TABLE 2. Outcome after esophagectomy according to location of the anastomosis, before and after propensity score matching

	Before matching (n = 2086)			After matching (n = 1308)			P for interaction by type of surgery¶¶
	Intrathoracic anastomosis (n = 928)	Cervical anastomosis (n = 1158)	P‡‡	Intrathoracic anastomosis (n = 654)	Cervical anastomosis (n = 654)	P‡‡	
Anastomotic leakage†			0.230			0.025	0.523
No	756 (81.5)	919 (79.4)		543 (83.0)	511 (78.1)		
Yes	172 (18.5)	239 (20.6)		111 (17.0)	143 (21.9)		
Pneumonia‡			0.688			0.408	0.267
No	598 (64.4)	756 (65.3)		421 (64.4)	432 (66.1)		
Yes	330 (35.6)	402 (34.7)		233 (35.6)	222 (33.9)		
Recurrent nerve paresis§			< 0.001			< 0.001	0.086
No	924 (99.6)	1063 (91.8)		650 (99.4)	608 (93.0)		
Yes	4 (0.4)	95 (8.2)		4 (0.6)	46 (7.0)		

Surgical reintervention¶			0.340			0.444	0.055
No	783 (84.4)	959 (82.8)		558 (85.3)	548 (83.8)		
Yes	145 (15.6)	199 (17.2)		96 (14.7)	106 (16.2)		
Duration of hospital stay (days)*	12 (3–172)	14 (3–386)	< 0.001§§	12 (3–145)	14 (4-386–22)	< 0.001§§	0.427
Duration of ICU stay (days)*	2 (0–125)	2 (0–155)	0.024§§	2 (0–125)	2 (0–155)	0.123§§	0.493
Postoperative death#			0.749			0.458	0.061
No	889 (95.8)	1106 (95.5)		633 (96.8)	628 (96.0)		
Yes	39 (4.2)	52 (4.5)		21 (3.2)	26 (4.0)		
Readmission**			0.991			0.494	0.674
No	794(85.6)	991 (85.6)		556 (85.0)	547 (83.6)		
Yes	134 (14.4)	167 (14.4)		98 (15.0)	107 (16.4)		
Positive resection margin††			0.497			0.618	0.780
No	877 (94.5)	1102 (95.2)		618 (94.5)	622 (95.1)		
Yes	51 (5.5)	56 (4.8)		36 (5.5)	32 (4.9)		
No. of lymph nodes harvested			0.752			0.223	0.070
< 20	444 (47.8)	546 (47.2)		356 (54.4)	334 (51.1)		
≥ 20	484 (52.2)	612 (52.8)		298 (45.6)	320 (48.9)		

Values in parentheses are percentages unless indicated otherwise; *values are median (full range). †Any clinically or radiologically proven anastomotic leakage. ‡Clinical manifestation of pneumonia or bronchopneumonia confirmed by a combination of radiological findings, leukocytosis, fever and/or positive sputum culture. §Any vocal cord dysfunction after resection. ¶Any postoperative surgical reintervention under general anesthesia. #Death during initial hospital admission or within 30 days after surgery. **Readmission to hospital within 30 days after initial discharge. †† The resection margin was evaluated using the College of American Pathologist criteria. . ‡‡c^2 test, except §§Mann–Whitney *U* test. ¶¶Stratified analysis for type of surgery (open approach *versus* minimally invasive approach)

TABLE 3. Characteristics of 3348 patients with esophageal cancer according to anastomotic leakage

		No anastomotic leakage (n = 2692)	Anastomotic leakage (n = 656)	P†	Missing§
Age (years)*		64.4(9.1)	65.4(8.5)	0.014‡	11 (0.3)
Sex	M	2087 (77.5)	519 (79.1)	0.379	1 (0.0)
	F	605 (22.5)	137 (20.9)		
BMI (kg/m^2)*		25.9(4.4)	26.1(4.3)		30 (0.9)
ASA fitness grade	I	487 (18.1)	90 (13.7)	< 0.001	23 (0.7)
	II	1656 (61.5)	369 (56.3)		
	III	541 (20.1)	191 (29.1)		
	IV	8 (0.3)	6 (0.9)		
COPD	No	2348 (87.2)	540 (82.3)	0.001	0 (0)
	Yes	344 (12.8)	116 (17.7)		
Coronary artery disease	No	2440 (90.6)	576 (87.8)	0.029	0 (0)
	Yes	252 (9.4)	80 (12.2)		
History of myocardial infarction	No	2522 (93.7)	597 (91.0)	0.015	0 (0)
	Yes	170 (6.3)	59 (9.0)		
History of arrhythmia	No	2490 (92.5)	582 (88.7)	0.002	0 (0)
	Yes	202 (7.5)	74 (11.3)		
Hypertension	No	1840 (68.4)	417 (63.6)	0.019	0 (0)
	Yes	852 (31.6)	239 (36.4)		
Peripheral vascular disease	No	2593 (96.3)	626 (95.4)	0.285	0 (0)
	Yes	99 (3.7)	30 (4.6)		
Diabetes mellitus	No	2302 (85.5)	524 (79.9)	< 0.001	0 (0)
	Yes	390 (14.5)	132 (20.1)		
History of stroke	No	2535 (94.2)	609 (92.8)	0.201	0 (0)
	Yes	157 (5.8)	47 (7.2)		

Thromboembolic events	No	2578 (95.8)	630 (96.0)	0.756	0 (0)
	Yes	114 (4.2)	26 (4.0)		
Endocrine disorder	No	2604 (96.7)	626 (95.4)	0.104	0 (0)
	Yes	88 (3.3)	30 (4.6)		
Previous abdominal or thoracic surgery	No	1881 (69.9)	457 (69.7)	0.917	0 (0)
	Yes	811 (30.1)	199 (30.3)		
Histology	ADC	2095 (77.8)	505 (77.0)	0.849	20 (0.6)
	SCC	528 (19.6)	135 (20.6)		
	Other	69 (2.6)	16 (2.4)		
Tumor location†	Proximal	28 (1.0)	16 (2.4)	0.015	23 (0.7)
	Middle	312 (11.6)	81 (12.3)		
	Distal	2352 (87.4)	559 (85.2)		
cT category	T1	154 (5.7)	41 (6.3)	0.568	163 (4.9)
	T2	543 (20.2)	126 (19.2)		
	T3	1896 (70.4)	458 (69.8)		
	T4	99 (3.7)	31 (4.7)		
cN category	N0	986 (36.6)	234 (35.7)	0.811	116 (3.5)
	N1	1131 (42.0)	287 (43.8)		
	N2	492 (18.3)	118 (18.0)		
	N3	83 (3.1)	17 (2.6)		
Neoadjuvant therapy	No	260 (9.7)	73 (11.1)	0.062	0 (0)
	nCT	205 (7.6)	34 (5.2)		
	nCRT	2227 (82.7)	549 (83.7)		

Values in parentheses are percentages unless indicated otherwise; Data shown in Table represent the data set after imputation. *values are mean(s.d.). †Proximal indicates less than 24 cm from teeth, middle indicates 24–32 cm from teeth, and distal more than 32 cm from teeth. COPD, chronic obstructive pulmonary disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy. ‡c^2 test, except ‡Student's *t* test. § number of missings for each variable before imputation.

TABLE 4. Results of multivariable logistic regression analysis assessing preoperative risk of developing anastomotic leakage after esophagectomy in 3348 patients with esophageal cancer

	Relative risk	*P*
ASA fitness grade		
I	1.00 (reference)	
II	0.99 (0.77, 1.30)	0.990
III	1.31 (1.09, 1.78)	0.009
IV	1.98 (1.27, 3.64)	0.026
COPD	1.21 (1.02, 1.45)	0.031
History of arrhythmia	1.25 (1.01, 1.55)	0.044
Diabetes mellitus	1.26 (1.06, 1.49)	0.009
Tumor location		
Proximal	1.86 (1.25, 2.77)	0.022
Middle	1.07 (0.87, 1.32)	0.514
Distal	1.00 (reference)	

Values in parentheses are 95 per cent confidence intervals. COPD, chronic obstructive pulmonary disease.

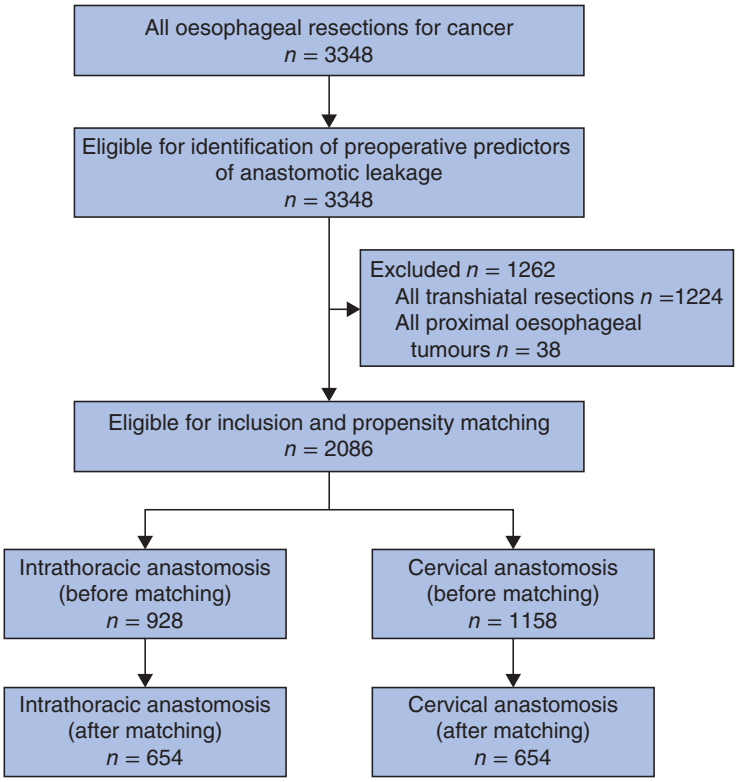

Figure 1. Study flow chart

DISCUSSION

This nationwide multicenter cohort study compared clinical outcome in patients with an intrathoracic *versus* cervical anastomosis following esophagectomy. An intrathoracic anastomosis was associated with lower rates of anastomotic leak and recurrent nerve paresis. This may explain the observed shorter duration of hospital stay among patients with an intrathoracic anastomosis than for those with a cervical anastomosis. However, among patients with an anastomotic leak, ICU and hospital stay was longer in the group with an intrathoracic anastomosis. Independent risk factors for anastomotic leakage include an ASA fitness grade of III or IV, history of cardiac arrhythmia, COPD, diabetes mellitus and proximally located tumors.

Four RCTS[18–21] have investigated clinical outcome in patients with an intrathoracic or cervical anastomosis. The results of these studies are equivocal regarding which anastomotic technique is preferred in reducing the risk of anastomotic leakage. The conflicting results can be explained by these studies being underpowered, with few events (range 2–13 events per study)[18–21], resulting in uncertain estimates. Other methodological shortcomings are the large degree of variation in surgical approaches, definitions of anastomotic leakage, and variation in stapled and hand-sutured anastomosis. Two meta-analyses[15,27], including 298 patients, found that anastomotic leakage occurred less often after an intrathoracic anastomosis than a cervical anastomosis. The present results are in line with these analyses.

Although the anastomotic leak rate was lower in patients with an intrathoracic anastomosis, and this may appear the preferred location of the esophagogastric anastomosis, leak rates in the present study are high compared with those in other studies[5,9]. Leak rates after an intrathoracic and cervical anastomosis range from 9 to 21 per cent[9,17,28,29] and 8 to 35 per cent[9,17,28,30] respectively. Some studies included only clinically relevant or radiologically proven anastomotic leaks, whereas others included both[31]. This discrepancy in definitions makes it difficult to compare leak rates between studies. In the present study, the definition of anastomotic leakage remained the same throughout the study, and included (subtle) clinical and radiological signs of leakage.

Between 2011 and 2016, some centers moved from a cervical to an intrathoracic anastomosis; 20.6 per cent of anastomoses were intrathoracic in 2011 and 59.3 per cent in 2015. The introduction of an intrathoracic anastomosis is associated with a learning curve[32,33]. Furthermore, the proportion of minimally invasive procedures increased from 53.1 to 85.4 per cent during the study period. The introduction of minimally invasive esophagectomy is also

associated with a learning curve when looking at reinterventions, morbidity and mortality[34,35]. Although propensity score matching equalled the difference in year of surgery and type of surgery between the groups, a potential learning curve may explain the high leak rate in the present study.

Despite a reduced risk of leakage and shorter hospital stay after an intrathoracic anastomosis, some surgeons prefer a cervical anastomosis. The possibility of a wider resection margin and less severe complications in patients with an anastomotic leak are claimed benefits of a cervical anastomosis[36]. The present study demonstrated that an anastomotic leak in a patient with an intrathoracic anastomosis led to a longer intensive care and hospital stay. This suggests that the clinical course in patients with an intrathoracic anastomotic leak is indeed more severe[37]. There were no differences in R0 resection rates, surgical reinterventions and postoperative mortality between intrathoracic and cervical anastomoses. The safety of the intrathoracic technique is supported by a recent meta-analysis[27] that found no difference in in-hospital mortality between intrathoracic and cervical anastomoses.

Previous studies[9,15,27,38] have defined factors associated with anastomotic leakage after an intrathoracic anastomosis. Factors resulting in poor tissue perfusion and vascular impairment are considered important[5,9,10,39]. This is in accordance with the present findings, as COPD, diabetes mellitus, ASA grades of III and IV, and proximal tumors were identified as independent risk factors for the development of anastomotic leakage. Although the present study did not identify risk factors other than those already described in the literature, these findings suggest that it may be important to improve the preoperative physical status of high-risk patients before esophagectomy.

Strengths of this study include the population-based design, the adjustment for important confounders, and the relatively large sample size. Furthermore, data from the DUCA are collected prospectively, and controlled for completeness and validity by an independent monitoring team. There are also limitations to this study, including its retrospective design and lack of randomization. Although propensity score matching was performed, the inability of propensity score matching to adjust for unknown confounders (such as surgical decision-making) is a limitation. Details of anastomotic techniques that may influence the healing of the anastomosis are not recorded in the DUCA. In addition, center- and surgeon-specific data on leak rates were not available for the purpose of this study, although these data are available for the individual centers. At present, a randomized trial[40] comparing the intrathoracic and

cervical approach is under way that should resolve these limitations and make an important contribution to the current literature.

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19

Diagnostic performance of a CT based scoring system for diagnosis of anastomotic leakage after esophagectomy: comparison with subjective CT assessment

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ABSTRACT

Objective

To develop a CT-based prediction score for anastomotic leakage after esophagectomy and compare it to subjective CT interpretation.

Methods

Consecutive patients who underwent a CT scan for a clinical suspicion of anastomotic leakage after esophagectomy with cervical anastomosis between 2003 and 2014 were analyzed. The CT scans were systematically re-evaluated by two radiologists for the presence of specific CT findings and presence of an anastomotic leak. Also, the original CT interpretations were acquired. These results were compared to patients with and without a clinical confirmed leak.

Results

Out of 122 patients that underwent CT for a clinical suspicion of anastomotic leakage; 54 had a confirmed leak. In multivariable analysis, anastomotic leakage was associated with mediastinal fluid (OR=3.4), esophagogastric wall discontinuity (OR=4.9), mediastinal air (OR=6.6), and a fistula (OR=7.2). Based on these criteria, a prediction score was developed resulting in an area-under-the-curve (AUC) of 0.86, sensitivity of 80%, and specificity of 84%. The original interpretation and the systematic subjective CT assessment by two radiologists resulted in AUCs of 0.68 and 0.75 with sensitivities of 52% and 69%, and specificities of 84% and 82%, respectively.

Conclusion

This CT-based score may provide improved diagnostic performance for diagnosis of anastomotic leakage after esophagectomy.

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide and the incidence rate is rapidly increasing[1]. Surgical resection of the esophagus with en-bloc lymphadenectomy combined with neoadjuvant chemoradiation or perioperative chemotherapy is the cornerstone of treatment for patients with locally advanced non-metastatic esophageal cancer[2-4]. Despite advances in surgical treatment and improvement in perioperative care anastomotic leakage remains a frequently encountered complication after esophagectomy with reported frequency rates of up to 30%[2,5]. Early detection of anastomotic leakage is crucial since delayed treatment is associated with significant morbidity, prolonged hospital stay, and mortality[6-9].

Several diagnostic modalities are available in case anastomotic leakage is clinically suspected, such as contrast swallow examination, endoscopy, or computed tomography (CT). Contrast swallow examinations are widely performed in order to assess anastomotic integrity. Although contrast swallow examinations are very specific, multiple studies have shown that they are of poor sensitivity, failing to identify significant anastomotic leaks[10-13]. Meanwhile, endoscopy after esophagectomy has proven to be a more accurate method to diagnose anastomotic leakage and provide information on the condition of the gastric tube[14,15]. However, most physicians are reluctant to utilize endoscopic examination early after esophagectomy as this invasive procedure may damage the anastomosis.

CT scanning is commonly performed for diagnosis of postoperative complications, since it is non-invasive and safe to use in critically ill patients. Previously, several studies have assessed the usefulness of CT scanning for the detection of anastomotic leakage after esophagectomy[13,16-18]. However, most of these studies assessed the diagnostic value of CT during postoperative routine screening and included only a small number of patients[13,16,17]. Also a wide range of diagnostic accuracies has been reported, suggesting that the association of different radiological findings after esophagectomy with anastomotic leakage is unclear[16-18]. Previous studies have shown that assessment of specific CT findings was useful for the prediction of anastomotic leakage after gastric and colorectal surgery[19,20].

In summary, objective criteria to detect anastomotic leakage on CT have not been clearly defined. Therefore, the purpose of this study was to determine reliable CT findings that can be used to diagnose anastomotic leakage and develop a CT-based risk prediction score for confirming or ruling out anastomotic leakage in a large cohort of patients with a clinical suspicion of leakage after esophagectomy. Also, the diagnostic performance of this CT-based

risk prediction score was compared to that of a systematic subjective evaluation by two expert radiologists and that of the original CT interpretation.

METHODS

Study population

This retrospective cohort study was approved by a institutional review board and the requirement to obtain informed consent was waived. The study was designed and conducted according to Standards for Reporting of Diagnostic Accuracy[21]. From a prospectively acquired database, all consecutive patients with esophageal or gastro-esophageal junction cancer who underwent an elective esophagectomy, between 2003 and 2014, at our tertiary referral center were identified. Within this database patients who were evaluated with a CT scan for a clinically suspected anastomotic leak after elective esophageal surgery were included. Surgical treatment consisted of a transthoracic or transhiatal esophagectomy with en-bloc lymphadenectomy and gastric tube reconstruction[22]. A cervical esophagogastric anastomosis was performed end-to-side with hand-sewn continuous sutures (3-0 PDS) in monolayer. After surgery two chest tubes were routinely placed, and removed during the following days in case of limited drainage (<200ml/24h), and absence of air leak.

Data collection

Clinical patient characteristics were extracted from the prospectively maintained database (Table 1). In addition, heart rate, temperature, white blood cell count (WBC) and C-reactive protein (CRP) were extracted from the patients' charts on the day anastomotic leakage was clinically suspected (day of CT scan). Anastomotic leakage was confirmed by either postoperative demonstration of saliva through the cervical wound, or visualization of anastomotic dehiscence or fistula during endoscopy or surgical re-intervention. The follow-up time was truncated to 30 days for all patients. All postoperative complications, including anastomotic leakage, were prospectively registered.

Image acquisition

Thoraco-abdominal CT images were acquired using commercially available 16- or 64-section CT scanners (Philips Medical Systems, Best, The Netherlands). Images were typically acquired with 64×0.625 millimeter section collimation, a tube rotation time of 500 milliseconds, a tube potential of 100 or 120 kV, an effective tube current of 120 mAs, and a pitch of 0.9 or 1.1. An iodinated 90-mL contrast material bolus was administered intravenously at 4 mL/sec in all patients. Oral contrast intake was not routinely used in our center as this was shown to have limited sensitivity for the detection of anastomotic leakage[13].

Variable selection

CT findings related to anastomotic leakage and esophageal surgery were selected for image analysis by two radiologists and two gastrointestinal surgeons during a consensus meeting. On the basis of their clinical experience, the most frequently encountered CT findings following esophageal surgery and variables described previously in the literature were included for analysis. The selected CT findings included mediastinal fluid collection, mediastinal air, mediastinal abscess (i.e. central zone of necrotic inflammatory material encapsulated by a discernible wall), and mediastinal induration (whenever the mediastinal fat showed non-contiguous, patchy inhomogeneity with water or low-hounsfield units soft tissue density [<20 hounsfield units]). When a mediastinal collection was present, the frequency, size of the largest collection, and the anatomical region (i.e. above the manubrium, between the manubrium and carina, between the carina and diaphragm, and below the diaphragm) were recorded. Other CT findings included a visible discontinuity of the esophagogastric wall, a fistula (scored if a fluid- or air-filled tract was visible between the esophagogastric anastomosis and another anatomic cavity [skin, trachea, pleural cavity or mediastinum]), pleural effusion, empyema (atypical pleural effusion, loculation in the pleural space, and thickening of the pleural membranes) and presence of a lung consolidation (i.e. atelectasis, pneumonia or non-specific).

Image evaluation

All CT scans were retrospectively reviewed together by two radiologists in consensus (with more than 25 and 6 years experience in gastrointestinal imaging, respectively). Images were reviewed on a picture archiving and communication system (Sectra AB, version 17.3, Linköping, Sweden). The reviewers knew that all patients had been subjected to an esophagectomy, but were blinded for the patients' detailed clinical information. The presence or absence of the various selected CT variables were systematically assessed and recorded. After the systematic assessment of the CT findings the reviewers also indicated if they suspected the patient to have an anastomotic leak (i.e. no anastomotic leak, a probable leak, or a definite anastomotic leak), further referred to as the systematic subjective assessment.

Also, all the original CT interpretations rendered as part of the clinical care were reviewed. Each CT report was originally interpreted by a board certified radiologist. The original interpretations were classified as 'no leak', 'probable leak', or 'definite leak'.

Statistical analysis and development of a practical scoring system

The association of clinical patient characteristics with anastomotic leakage was studied univariably. Categorical parameters were compared using the chi-square test or Fisher's exact

test in case of small cell counts. The Student's T-test and Mann-Whitney-U test were used to compare groups with and without anastomotic leakage for parametric and non-parametric continuous parameters, respectively. In order to analyze whether the different CT findings were associated with anastomotic leakage, univariable logistic regression models were used providing odds ratios (ORs) with 95% confidence intervals (CIs). Subgroup analyses were performed to assess whether location in the mediastinum and days after surgery influenced the associations of the different CT findings with anastomotic leakage.

Subsequently, parameters with a *p*-value below 0.05 in univariable logistic regression analysis were entered into a multivariable logistic regression model with backward stepwise selection to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage. A practical scoring system was developed using the *beta*-regression coefficients of the retained predictive factors.

To compare diagnostic performances of the different CT assessments, receiver operating characteristics (ROC) curve analysis was performed and the area-under-the-curves (AUC) were computed. Ideal cut-off values were calculated by giving equal weight to sensitivity and specificity. In addition, the potential superiority of the prediction score in comparison with the systematic subjective and original assessment was evaluated using the net reclassification index (NRI). The NRI reflects the reclassification ability of the model and is the sum of improvement in correctly predicting patients with and without leakage[23]. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Demographics

In the study period a total of 405 patients underwent esophagectomy with gastric tube reconstruction. Of these patients, 283 were excluded because there was no clinically suspected leak (n=238), no CT scan was performed in case of a suspected anastomotic leak (n=43) or the CT scan was of insufficient quality (n=2). Consequently, 122 patients were deemed eligible for inclusion in our study, of whom 54 (44.3%) had a confirmed anastomotic leak (Figure 1).

Clinical and treatment-related patient characteristics and their univariable association with anastomotic leakage are summarized in Table 1. None of the studied patient and treatment-related factors were significantly associated with the occurrence of anastomotic leakage. The median time interval between esophagectomy and CT acquisition was 6 days (range:

1-32). Anastomotic leakage occurred after a median time of 8 days (range: 1-22) following esophagectomy. Anastomotic leakage was confirmed by, endoscopy (n=10), surgical re-intervention (n=31) or demonstration of saliva during opening of the cervical wound (n=13). Treatment of anastomotic leakage consisted of ceasing oral intake in combination with opening of the cervical wound (n=20), placing a stent (n=3) or surgical re-intervention (n=31).

Predictors of anastomotic leakage

The results of univariable logistic regression analyses for each specific CT finding in relation to anastomotic leakage are presented in Table 2. In univariable analyses studying specific CT findings, presence of a mediastinal fluid collection (OR 3.1, 95% CI: 1.4–7.1, p=0.006) and mediastinal air (OR 11.1, 95% CI: 3.6–34.2, p<0.001) were significantly associated with anastomotic leakage.

In subgroup analyses the associations of mediastinal fluid with anastomotic leakage was independent its size, anatomic location within the mediastinum, and the number of days they occurred after surgery. In subgroup analyses of patients with presence of mediastinal air on their postoperative CT scan (70%, 86/122), the number of days after surgery that air was observed was significantly associated with anastomotic leakage (OR for each additional postoperative day: 1.162, 95% CI: 1.022–1.327, p=.022). To this regard, the prevalence of a confirmed leak in patients with observed free air before or after the 7th postoperative day was 50% and 73%, respectively. Of the patients with free air in the mediastinum, air was observed above the manubrium in 22 patients (12/22, 55% leakage), between the manubrium and carina in 4 patients (3/4, 75% leakage), between carina and diaphragm in 8 patients (4/8, 50% leakage), and in a combination of these anatomic locations in 52 patients (31/52, 60% leakage). The association of mediastinal air with anastomotic leakage was independent of its location (p=0.838). Also the size of mediastinal air on CT was not associated with anastomotic leakage.

In addition, presence of wall discontinuity (OR 12.6, 95% CI: 4.39–36.20, p<0.001), fistula (OR 12.7, 95% CI: 2.8–58.5, p<0.001) and empyema (OR 17.1, 95% CI: 2.1–137.6, p=0.007) were significantly associated with anastomotic leakage. No significant difference in incidence of other CT findings among patients with or without anastomotic leakage was found.

In multivariable logistic regression analysis, a mediastinal fluid collection (OR 3.4, 95% CI: 1.3–9.4, p=0.016), mediastinal air (OR 6.6, 95% CI: 1.9–23.2, p=0.003), wall discontinuity (OR 4.9, 95% CI: 1.5–15.9, p=0.008), and presence of a fistula (OR 7.2, 95% CI: 1.2–43.8, p=0.032)

remained independently and significantly associated with anastomotic leakage (Table 3, Figure 3). The association between empyema and anastomotic leakage was no longer significant after multivariable adjustment (p=0.093).

Systematic subjective CT assessment

During systematic subjective CT scan assessment by the radiologists, a leak was suggested in 49 patients of which 37 (75.5%) had a confirmed leak, whereas absence of a leak was scored in 53 patients of which 10 (18.9%) had a confirmed leak. Of the remaining patients with a probable leak (n=20), 7 (35%) had a confirmed leak. The radiologists evaluation, referred to as 'systematic subjective assessment', yielded an AUC of 0.75 (95% CI: 0.66–0.84) in ROC analysis (Figure 2, Table 4). Sensitivity and specificity of the systematic subjective assessment by the radiologists (no + probable leakage versus presence of leakage) were 68.5% (37 of 54; 95% CI: 54.3-80.1) and 82.4% (56 of 68; 95% CI: 70.8-90.1), respectively (Table 4).

Original clinical CT interpretation

The original clinical CT interpretation yielded an AUC of 0.68 (95% CI: 0.59-0.78) in ROC analysis (Figure 2, Table 4). Sensitivity and specificity of the original assessment by the radiologists (absence of leakage versus probable + presence of leakage) were 51.9% (28 of 54; 95% CI: 38.0-65.5) and 83.8% (57 of 68; 95% CI: 72.5-91.3), respectively (Table 4).

Risk scoring system

An anastomotic leakage prediction score (ALP score) was constructed based on the 4 CT findings that remained significantly associated with anastomotic leakage in multivariable analysis. Based on the absolute *beta*-regression coefficient, presence of each variable was converted into a corresponding amount of points rounded to its nearest integer. Next scaling was performed with respect to the discriminatory power of the scores as determined by ROC analysis. To this regard it proved feasible to assign one point for the presence of each predictive factor – in order to keep the score simple – without compromising its discriminative ability (Table 3). Therefore, the cumulative amount of points of the ALP score ranges from 0 to 4. The diagnostic performance of the possible scores for identifying an anastomotic leak are presented in Table 5.

Using ROC analysis a total of 2 points was statistically determined as optimal cut-off, in which patients with scores ≥2 points were considered at high risk of anastomotic leakage. The cut-off value of ≥2 points yielded a sensitivity of 80% (43 of 54; 95% CI: 66.1–88.9) and specificity

of 84% (57 of 68; 95% CI: 72.5–91.3). The final ALP score model had an AUC of 0.86 (95% CI: 0.79-0.93) (Figure 2, Table 4).

The ALP scoring system improved the AUC (0.86 versus 0.75 and 0.68) with an NRI of 12.5% (p=0.008) and 27.7% (p<0.001) for the detection of anastomotic leakage compared to the systematic subjective CT assessment and original CT interpretation, respectively (Table 4). These findings indicate that with the ALP score 11.1% and 27.7% of the patients with definite anastomotic leakage, and 1.4% and 0% of patients without leakage were better classified compared to the systematic subjective CT assessment and original CT interpretation, respectively.

TABLE 1. Clinical and treatment-related characteristics in relation to anastomotic leakage

Characteristic	**Anastomotic leakage (n = 54)**	**No anastomotic leakage (n = 68)**	***p* value**
Male gender	41 (75.9)	56 (82.4)	0.382
Age (years)*	65.2 ± 9.0	65.8 ± 8.9	0.708
BMI (kg/m^2)*	25.7 ± 4.4	26.8 ± 4.3	0.158
ASA score	12 (22.2)	12 (17.6)	0.841
I	28 (51.9)	40 (58.8)	
II	14 (25.9)	15 (22.1)	
III	0 (0.0)	1 (1.5)	
IV			
COPD	13 (24.1)	10 (14.7)	0.189
Cardiac co-morbidity	15 (27.8)	23 (33.8)	0.474
Diabetes mellitus	9 (16.7)	15 (22.1)	0.457
Current smoker	17 (31.5)	21 (30.9)	0.898
Neoadjuvant therapy			0.973
None	16 (30.9)	21 (29.6)	
Chemotherapy	12 (22.6)	14 (21.2)	
Chemoradiotherapy	26 (49.1)	33 (50.0)	
Heart rate*†	103 ± 22	96 ± 19	0.085
Temperature*ǂ	37.7 ± 0.8	37.7 ± 0.8	0.950
Leukocytes*§	16.2 ± 7.1	15.6 ± 7.3	0.385
C-reactive protein*‖	224 ± 104	194 ± 96	0.110

Note. Data are numbers of patients with percentages in parentheses.*Data are mean ± standard deviation. †Heart rate in beat per minute. ǂTemperature in Celcius (*°C).* §Number of leukoctyes x 10 ^{9}/L. ‖CRP in mg/L

TABLE 2. Univariable logistic regression analysis of specific postoperative CT findings in relation to anastomotic leakage after esophagectomy

Characteristic	Anastomotic leakage (n=54)	No anastomotic leakage (n = 68)	OR (95% CI)	p value
Mediastinal				
Induration	7 (13.0)	6 (8.8)	1.5 (0.49-4.88)	0.464
Fluid collection	23 (42.6)	13 (19.1)	3.1 (1.40-7.06)	0.006*
Abscess	7 (13.0)	4 (5.9)	2.4 (0.66-8.61)	0.185
Air	50 (92.6)	36 (52.9)	11.1 (3.61-34.20)	<0.001*
Wall discontinuity	27 (50.0)	5 (7.4)	12.6 (4.39-36.20)	<0.001*
Fistula	15 (27.8)	2 (2.9)	12.7 (2.76-58.47)	<0.001*
Pleural effusion	46 (85.2)	58 (85.3)	1.0 (0.36-2.71)	0.987
Empyema	11 (20.4)	1 (1.5)	17.1 (2.1-137.6)	0.007*
Atelectasis	50 (92.6)	59 (86.8)	1.9 (0.55-6.57)	0.306
Pulmonary infiltrate	11 (20.4)	19 (27.9)	0.7 (0.28-1.54)	0.336

Note – Data presented as counts with percentages in the parentheses. *Significant difference between patients with versus without anastomotic leakage (p<0.05). OR: odds ratio. CI: confidence interval

TABLE 3. Multivariable logistic regression analysis of CT findings significantly associated with anastomotic leakage in univariable analysis

Characteristic	β regression coefficient	OR (95% CI)	p value	Points†
Fluid collection	1.233	3.43 (1.26-9.34)	0.016*	1
Air cavity	1.882	6.57 (1.86-23.21)	0.003*	1
Wall discontinuity	1.591	4.91 (1.52-15.88)	0.008*	1
Fistula	1.973	7.19 (1.18-43.84)	0.032*	1
Empyema	1.987	7.29 (0.72-74.30)	0.093	NA

*Significant difference between patients with versus without anastomotic leakage (p<0.05). OR: odds ratio, CI: confidence interval. †Assignment of points to CT findings was based the corresponding β regression coefficient. Scaling was performed with respect to the discriminatory power of the scores as determined by ROC analysis.

TABLE 4. Receiver operating characteristics analysis and net reclassification index (NRI) estimates for anastomotic leakage according to the original interpretation, subjective CT assessment and the anastomotic leakage prediction model

Model	AUC (95% CI)	Ideal cut-off	SE (%)	SP (%)	PPV (%)	NPV (%)	NRI (%)
Original CT interpretation	0.68 (0.59-0.78)	No AL vs. probable or definite AL	51.9	83.8	71.8	68.7	reference
Systematic assessment	0.75 (0.66-0.84)	No or probable AL vs. definite AL	68.5	82.4	75.5	76.7	15.2
ALP-score model	0.86 (0.79-0.92)	Score ≥2 vs. score <2	79.6	83.8	81.1	83.8	27.7

ALP-score: anastomotic leakage prediction score. AL: anastomotic leakage. AUC: area under the curve. SE: sensitivity. SP: specificity. PPV: positive predictive value. NPV: negative predictive value. NRI: Percentage of net reclassification index.

TABLE 5. Risk scores and their coordinates on the ROC curve

Risk score	n	Observed leakage risk	Sensitivity* (%)	Specificity* (%)
Anastomotic leakage prediction score				
ALP score 0	27	7.4% (2/27)	100	0
ALP score 1	41	22.0% (9/41)	96.3	36.8
ALP score 2	29	72.4% (21/29)	79.6	83.8
ALP score 3	17	82.4% (14/17)	40.7	95.6
ALP score 4	8	100 % (8/8)	14.8	100
Systematic subjective assessment				
No leakage	53	18.9% (10/53)	100	0
Probable leakage	20	35.0% (7/20)	81.5	63.2
Presence of leakage	49	75.5% (37/49)	68.5	82.4
Original CT interpretation				
No leakage	83	31.3% (26/83)	100	0
Probable leakage	14	64.3% (9/14)	51.9	83.8
Presence of leakage	25	76.0% (19/25)	35.2	91.2

ROC: receiver operating characteristics.
* Sensitivity and specificity defined by their coordinates on the ROC curve.

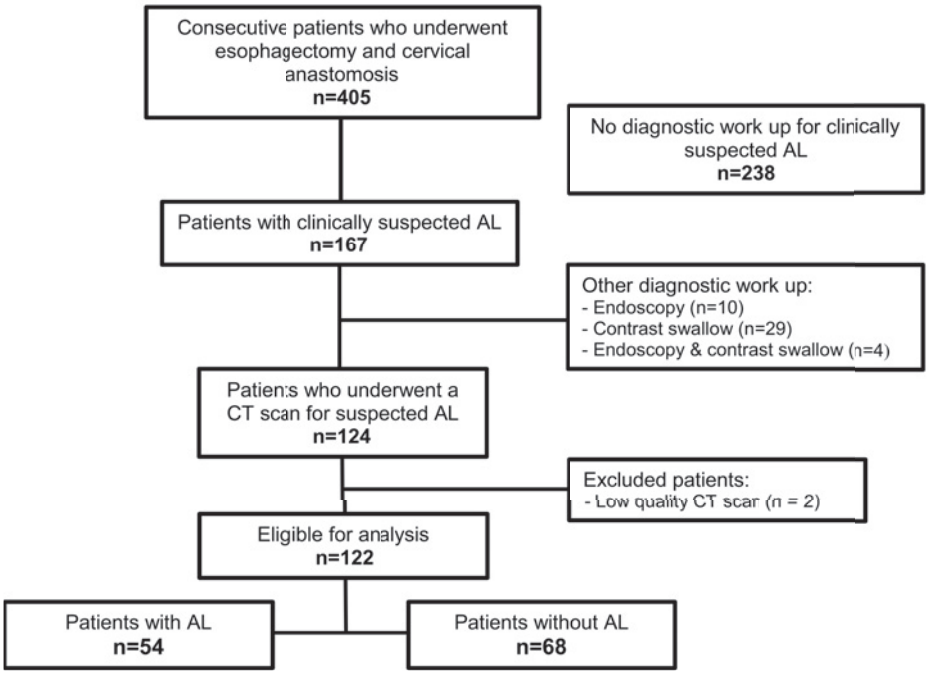

Figure 1. Flowchart demonstrates the selection process of patients with a suspicion of anastomotic leakage (AL).

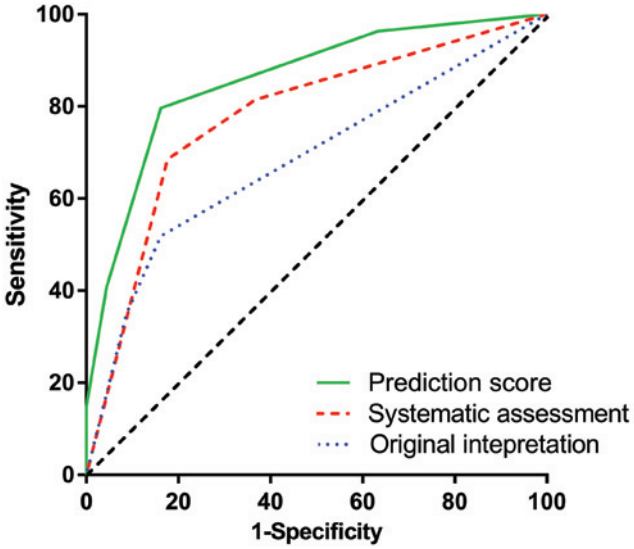

Figure 2. ROC curve analysis of the 'anastomotic leakage prediction score' (green line), the systematic subjective CT assessment by expert radiologists (red dotted line) and the original interpretation (blue dotted line) indicating their ability to discriminate between patients with and without anastomotic leakage.

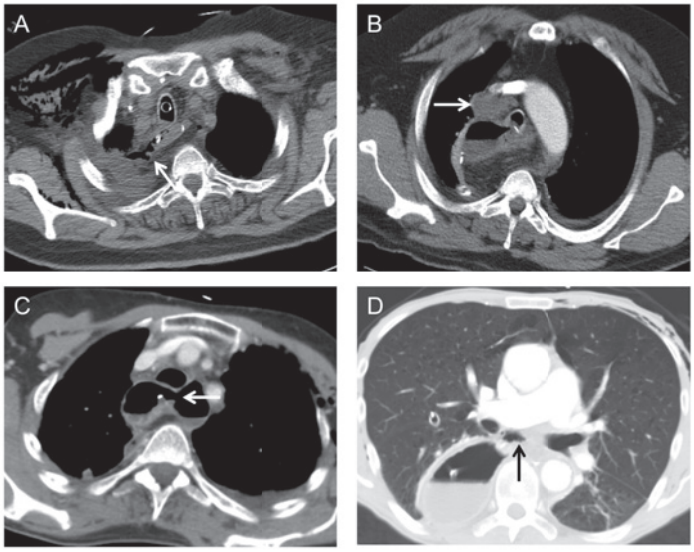

Figure 3. Examples of CT findings associated with the presence of anastomotic leakage after esophagectomy. **A:** Image shows a fistula between the gastric tube and right pleural cavity (*arrow*). **B:** Image shows a fluid collection (*arrow*) in the mediastinum. **C:** Image shows a visible discontinuity of the esophagogastric wall (*arrow*). **D:** Image shows a mediastinal air cavity (*arrow*) after esophagectomy.

DISCUSSION

In this retrospective cohort study CT findings of patients with a clinically suspected anastomotic leak after esophagectomy were systematically analyzed and predictors of anastomotic leakage were identified. Presence of mediastinal fluid, mediastinal air, esophagogastric wall discontinuity and fistula were independently associated with anastomotic leakage, irrespective of clinical and treatment-related patient characteristics. Based on these CT findings a prediction score for anastomotic leakage was developed. The 4-point ALP score demonstrated good diagnostic performance. This study demonstrates superior diagnostic accuracy of a CT-based scoring system in comparison with the systematic subjective assessment (NRI: 12.5%), and original CT interpretation (NRI: 27.7%) of leakage on a post-esophagectomy CT scan. The easy to use point-based ALP score may provide radiologists and surgeons a tool to objectively assess the risk of anastomotic leakage after esophageal surgery in patients with a suspicion of such complication.

CT scanning is increasingly being performed for the detection of anastomotic leakage after esophagectomy, since it is non-invasive, safe in critically ill patients, and aids in the detection of other associated findings (e.g. pulmonary complications)[16,17]. However, the interpretation of a CT scan after prior esophageal resection remains difficult due to the anatomic changes and residual air and fluid shortly after surgery. Previous studies have assessed the diagnostic value of CT scanning for the detection of anastomotic leakage after esophagectomy[13,16-18]. In most of these studies 1 or 2 reviewers determine their own definition as to what an anastomotic leak on a CT scan consists of, without assessing specific CT findings[16,17]. In the literature this results in a large difference in reported diagnostic values[16,17]. This observation is confirmed by the current study in which a difference of 17% in sensitivity was found between the original CT interpretation and the systematic subjective CT assessment. These findings are suggestive for a lack of consensus on radiographic findings associated with anastomotic leakage in patients after esophagectomy.

Until now, two studies have made a similar attempt to identify specific CT findings for the detection of anastomotic leakage after esophagectomy[13,18]. One study that included 97 patients assessed several specific CT findings during postoperative routine screening. In that study presence of mediastinal air and contrast leakage on postoperative day 3 and 7 were associated with anastomotic leakage[13]. Another study that included 54 patients found mediastinal air and mediastinal fluid to be associated with anastomotic leakage[18]. These observations partially correspond with the results of our study that found an association of anastomotic leakage with mediastinal air and fluid collections. However, in these two previously mentioned studies only

few events of anastomotic leakage occurred (n=11 and n=6, respectively), which results in an uncertainty of estimates[13,18]. Interestingly, these studies show that using solitary CT findings as diagnostic marker, without combining them in a model, results in either low sensitivity or low specificity. Contrast leakage after esophagectomy, for example, is known to be a specific finding but the absence of extravasation of contrast is associated with high false-negative rates and consequently a low sensitivity [13]. On the contrary, presence of mediastinal air near the gastric tube is very sensitive, but since this is a common finding after esophageal surgery it is not very specific [13, 18]. Our data suggest that combining specific CT findings in a risk score could be used to overcome these limitations and improve diagnostic accuracy of CT scanning after esophagectomy.

The developed ALP score has a good predictive value and includes well-recognized CT findings. The data indicate that in the presence of 2 or more of 4 CT findings the decision whether to start treatment could be made quite reliably, without true additional value of other diagnostic tests. This could lead to a reduction in treatment delay that is associated with additional tests. Although the cut-off point of ≥2 yielded the highest overall discriminatory value, each additional point was associated with an increased risk, and clinical reasoning (particularly with scores of 1 and 3) remains important for treatment decision-making. To this regard, endoscopy after esophagectomy may be useful in cases where the results of the CT-scan are uncertain. Endoscopy has proven to be an accurate method to diagnose anastomotic leakage[14,15].

In the current study in appeared counterintuitive that empyema fell out of the multivariable model, as it was highly predictive in univariable analysis. However, in multivariable prediction modeling the outcome (anastomotic leakage) is predicted based on values of a set of predictor variables (CT parameters). This method allows us to assess the impact of multiple predictor variables in the same model. In the current series at least 2 or more predictor variables that were highly suggestive for anastomotic leakage (i.e. fluid collection, air cavity, wall discontinuity, and fistula) were present in all 12 patients with empyema. Therefore, the added value of empyema - over the other predictor variables - for the prediction of anastomotic leakage was redundant in the current model, and therefore lost its significance. However, the fact remains that in clinical practice the presence of empyema on a postoperative CT scan is highly suggestive for the presence of an anastomotic leak.

Various limitations apply to this study. First, this study is limited by its retrospective nature. Second, the specific CT findings may be subject to interobserver variability. Standardization

of mediastinal CT findings may overcome this problem. Finally, external validation of the prediction score is warranted since there is a risk of model overfitting due to multiple testing and differences with other patient populations (e.g. prevalence of leakage, use of other surgical techniques).

In conclusion, this study demonstrates that the presence of mediastinal fluid, mediastinal air, esophagogastric wall discontinuity and a fistula on a postoperative CT scan are independently and significantly associated with anastomotic leakage after esophagectomy in patients with a clinical suspicion of anastomotic leakage. Based on these items a CT-based anastomotic leakage prediction score was developed with superior discriminatory ability compared to systematic subjective CT assessment and original CT interpretation for the detection of anastomotic leakage after esophagectomy.

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Summary

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At present, the incidence of esophageal adenocarcinoma continues to rise and will form an increasingly large health burden in the years ahead. Action is needed to curb this "quiet epidemic". Despite remarkable progress in available treatment strategies during the last decade, some patients that opt for curative therapy remain unresponsive to treatment. One of the primary reasons why not all patients respond to – or some suffer from – the currently available treatment regimens can be attributed to high inter-patient variability in response to such treatment (Chapter 1). Therefore, the key to successful improvement of healthcare outcomes is to take this inter-patient variability into consideration to design a successful treatment plan. The studies presented in this thesis aimed to reduce treatment related morbidity and ensure maximal benefit of treatment by optimizing patient selection and improve the use of existing diagnostic and therapeutic tools. To achieve this aim, improvements were proposed with regard to staging (Part 1), treatment response prediction (Part 2), and in the management of postoperative complications (Part 3). In this chapter the findings of the studies presented in this thesis are summarized.

PART I. STAGING

Chapter 2. Cervical lymph node imaging

The introduction of integrated PET/CT scanning has improved the accuracy of cancer staging by providing both anatomical and metabolic information. In this study the additional diagnostic value of cervical ultrasonography to PET/CT for the detection of cervical lymph node metastases was evaluated in a cohort of esophageal cancer patients treated in the University Medical Center Utrecht. No additional diagnostic value of cervical ultrasonography for this purpose was found. This finding indicates that routinely performing cervical ultrasonography during the standard diagnostic work-up of esophageal cancer patients can be considered unnecessary.

Chapter 3. Detection of interval metastasis

Accurate preoperative detection of interval metastasis of esophageal cancer is crucial for optimal selection of patients suitable for surgery. Findings in the current cohort study demonstrated that PET/CT restaging after neoadjuvant chemoradiotherapy detects interval metastases in 8% of patients. Independent risk factors for the development of interval metastases were clinical nodal involvement, tumor length, tumor histology, and baseline SUV_{max}. Based on these findings a prediction score was developed that can help physicians to prioritize additional restaging modalities for patients most likely to benefit.

Chapter 4. Treatment of clinical T2N0 tumors

The benefit of neoadjuvant chemoradiotherapy for locally advanced esophageal cancer is well-established, but remains unclear for patients with clinical T2N0 tumors. In this nationwide multi-center cohort study current clinical staging was evaluated and outcomes of neoadjuvant chemoradiotherapy were compared to a surgery alone approach for patients with clinical T2N0 esophageal cancer. Compared to surgery alone, neoadjuvant chemoradiotherapy achieved higher radical resection rates and improved survival. At the same time clinical staging proved to be highly inaccurate. These results indicate that – until clinical staging improves significantly – neoadjuvant chemoradiotherapy followed by surgery should be preferred as treatment strategy for patients with clinical T2N0 esophageal cancer.

Chapter 5. PET/CT for the detection of recurrent esophageal cancer

The interpretation of conventional diagnostic modalities such as CT and endoscopy for the detection of recurrent disease is often difficult due to local anatomic changes caused by surgery. PET/CT may overcome this limitation by by providing both anatomical and metabolic information. Therefore, this study systematically reviewed and meta-analyzed the diagnostic performance of PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent. The results revealed that PET/CT is a reliable imaging modality with a high sensitivity (96%) and moderate specificity (78%). This indicates that in case recurrent disease is clinically suspected, the imaging method of choice should be PET/CT as it allows for a minimal false-negative rate. However, histopathologic confirmation of suspected lesions remains required, since a considerable false positive rate was noticed.

Chapter 6. Prediction of early recurrence

In patients who suffer from early disease recurrence within 1-year of completing neoadjuvant chemoradiotherapy followed by surgery, the benefit of surgery would probably not outweigh its potential side-effects. Some suggest that consideration should therefore be given to less invasive treatment strategies in patients who are likely to have early recurrence after surgery. Therefore, in this chapter a preoperative prediction model was developed – based on gender, histologic grade, signet ring cell adenocarcinoma, clinical tumor stage, and baseline SUV_{max} – that predicts early recurrence risk. By using this scoring system before surgery, treating physicians could generate individualized predictions of early recurrence risk. As such, identifying subgroups of patients with different risks of early recurrence may impact shared treatment decision-making and choices of care. However, before this prediction score can be safely implemented in clinical practice, external validation and improvement with novel predictors is warranted.

Chapter 7. Prediction of overall survival

Timely and accurate prediction of mortality risk after neoadjuvant chemoradiotherapy and surgery may guide risk-stratified follow-up strategies and prompt earlier initiation of interventions to improve survival. This study externally validated a previously published nomogram for the prediction of 5-year overall survival after neoadjuvant chemoradiotherapy with subsequent surgery in an independent international cohort of 975 esophageal cancer patients. The nomogram showed reasonable discrimination – comparable to the initial publication – and calibration showed excellent agreement between predicted and actual observed overall survival estimates. Therefore, the current validated model can be used to risk-stratify adjuvant treatment allocation and identify patients in need of routine surveillance after treatment.

PART 2. TREATMENT RESPONSE PREDICTION

Chapter 8. Correlation between functional imaging markers of DW-MRI and PET/CT

Both the apparent diffusion coefficient (ADC) acquired by DW-MRI and the standardized uptake value (SUV) acquired by PET/CT are well-established functional parameters in cancer imaging. Until recently it was unclear whether these two markers may provide complementary prognostic and predictive information in esophageal cancer. Therefore, in this prospective study of 76 patients, correlation between tumor ADC and SUV values as measures of cell density and glucose metabolism were evaluated. Negligible non-significant correlations were found. This finding indicates that both tumor cellularity measured by DW-MRI imaging and tumor metabolism by PET/CT are independent cellular phenomena in newly diagnosed esophageal cancer. As such, ADC and SUV values likely have complementary roles as imaging markers in the prediction of survival and evaluation of response to treatment in esophageal cancer.

Chapter 9. Multimodality MRI for treatment response prediction

Two recent pilot studies of our study group reported that tumor alteration on both DW-MRI and DCE-MR imaging during the first 2-3 weeks of neoadjuvant chemoradiotherapy are highly predictive for pathologic tumor response to neoadjuvant treatment. This study assessed whether combining data from both DW-MRI and DCE-MRI in 45 patients receiving neoadjuvant chemoradiotherapy for esophageal cancer yields complementary information for response prediction, and may therefore increase predictive power compared to single modality MR imaging. Indeed, multivariable logistic regression analyses showed complementary value when combining DW-MRI and DCE-MRI for the prediction of treatment response (c-statistic = 0.89). Unfortunately many patients had to be excluded from this analysis due to

poor scan quality. Therefore, our research group recently invested in improving scan quality and designed a large multicenter study to validate these results and determine the exact value of both modalities in this setting.

Chapter 10. Patient perspectives on repeated MRI and PET/CT examinations

With the current increase in repeated imaging strategies for disease monitoring during treatment, the perceived burden of diagnostic tests by patients warrants attention. In this study of 27 patients the experienced burden of repeated MRI and PET/CT examinations during neoadjuvant treatment was evaluated with a self-report questionnaire. Few patients experienced discomfort, pain, anxiety, and embarrassment during MRI and PET/CT imaging. When asked to rank different tests, patients preferred MRI over PET/CT (67% versus 22%, respectively, $p = 0.023$). As such, from a patient perspective both MRI and PET/CT are generally well-tolerated and could both be used for the assessment of response to treatment in esophageal cancer patients.

PART 3. POSTOPERATIVE COMPLICATION MANAGEMENT

Chapter 11. Costs of complications

In order to develop and prioritize quality improvement initiatives drivers of costs of esophagectomy have to be identified. An analysis of prospectively collected clinical and financial outcomes after esophageal cancer surgery at the University Medical Center Utrecht revealed that the average total cost for one esophagectomy was €37,581. The estimated costs of an esophagectomy without complications were €23,476, whereas those with severe complications (29%) were €59,167. Although not all postoperative complications can be prevented, these results indicate that the implementation of preventive measures to reduce complications could also result in a considerable cost reduction.

Chapter 12. Clinical impact of complications

In order to optimally allocate healthcare resources, complication-related quality initiatives should target those complications that have the greatest overall impact on outcomes after surgery. The impact of specific postoperative complications on clinical outcomes after esophagectomy were assessed in all patients that underwent esophageal surgery in the Netherlands between 2011 and 2016 (n = 4096). Compared to other complications, anastomotic leakage and pulmonary complications had the greatest overall impact on postoperative mortality, prolonged hospitalization, reoperations, and hospital readmission. As such, complication-related quality initiatives that can successfully reduce the incidence of these complications will have the greatest overall clinical benefit for patients.

Chapter 13. Calcification of arteries supplying the gastric tube and the risk of anastomotic leakage

Recently our research group identified atherosclerotic calcification of the locoregional arteries supplying the gastric tube as independent risk factor for anastomotic leakage after esophagectomy. In order to validate this new risk factor its generalizability was assessed in an independent cohort of patients in Almelo and Eindhoven. Atherosclerotic calcification of the thoracic aorta was confirmed as an independent risk factor for anastomotic leakage after esophagectomy. The proposed calcification scoring system may aid in patient selection and lead to earlier diagnosis of this potentially fatal complication.

Chapter 14. Generalized calcification and the risk of anastomotic leakage

In the previous chapter it was demonstrated that calcification of arteries supplying the gastric tube is associated with anastomotic leakage after esophagectomy. However, it remained unclear whether this association only derived from local flow limitations, or vascular disease in general. In this study it was demonstrated that calcification of the coronary and supra-aortic arteries were more predictive of anastomotic leakage compared to local arteries supplying the gastric tube. These results suggest that generalized vascular disease is more indicative for the risk of leakage than local vascular disease. This new described risk factor for anastomotic leakage may be used in future prediction models, and eventually aid to a more individualized identification of anastomotic leakage risk.

Chapter 15. Perioperative risk factors for anastomotic leakage and pneumonia

Recognition of the influence of intraoperative and postoperative clinical parameters on the occurrence of the two most frequently encountered complications after esophagectomy (i.e. pneumonia and anastomotic leakage) could contribute to the development of intraoperative and postoperative preventative approaches. In this study extensive measurements of hemodynamic and respiratory factors during and early after esophagectomy were performed. A lower minimum intraoperative pH (below 7.25) was found to be significantly associated with anastomotic leakage, whereas a low average mean arterial pressure was related to pneumonia. These findings may be used to set and protect specific perioperative cardiorespiratory goals that may lead to a reduction in postoperative complications.

Chapter 16. Perioperative chemotherapy versus neoadjuvant chemoradiotherapy

After the introduction of neoadjuvant chemoradiotherapy in clinical practice, several hospitals reported a vast increase in their postoperative complication rate. Therefore, this study compared the two most frequently applied multimodality treatment strategies in locally advanced esophageal adenocarcinoma with regard to treatment-related toxicity, postoperative morbidity, pathologic outcome, and survival. Both chemoradiotherapy and chemotherapy were associated with substantial regimen-specific adverse events. No significant differences regarding postoperative morbidity and mortality were found. Although neoadjuvant chemoradiotherapy significantly improved pathologic response rates and reduced the risk of locoregional recurrence, these results did not translate into an overall survival benefit.

Chapter 17. Radiation dose to the gastric fundus and the risk of anastomotic leakage

As mentioned in the summary of the previous chapter, concerns have been raised that neoadjuvant chemoradiotherapy could contribute to an increased risk of postoperative complications. The current Chapter indeed demonstrated that neoadjuvant radiation dose to the gastric fundus is associated with anastomotic leakage in patients treated with neoadjuvant chemoradiotherapy with subsequent esohpagectomy for esophageal cancer. This finding is important for clinical practice because it suggests that efforts should be made to minimize radiation dose to the gastric fundus when planning neoadjuvant chemoradiotherapy for esophageal cancer.

Chapter 18. Cervical versus intrathoracic anastomosis

Studies comparing the anastomotic leak rate in patients with an intrathoracic versus a cervical anastomosis after esophagectomy are equivocal. Accordingly, outcomes after esophagectomy in patients with an intrathoracic or cervical anastomosis were compared in patients that underwent esophageal surgery in the Netherlands between 2011 and 2015 (n = 3348). Propensity score matching was used to adjust for potential confounders. An intrathoracic anastomosis was associated with a lower leak rate than a cervical anastomosis. The percentage of patients with recurrent nerve paresis was also lower and an intrathoracic anastomosis was associated with a shorter median hospital stay.

Chapter 19. Diagnosis of anastomotic leakage with CT

Objective criteria to detect anastomotic leakage on CT have not been clearly defined. This study demonstrated that the presence of mediastinal fluid, mediastinal air, esophagogastric wall discontinuity and a fistula on a postoperative CT scan are suggestive for the presence of an anastomotic leak. Based on these items a CT-based anastomotic leakage prediction score

was developed that provides superior discriminatory ability for detecting anastomotic leakage compared to conventional interpretation methods.

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General discussion

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The aim of this thesis was to contribute to the improvement of staging (Part 1), treatment response prediction (Part 2) and complication management (Part 3) for patients with esophageal cancer. Some findings have already changed – or provide a basis for changes in – the perioperative management of these patients. In this chapter, the potential and challenges of these findings in clinical practice and future perspectives are discussed.

STAGING

Clinical staging

It all begins with staging. Assigning the right treatment strategy to the right patient is only possible if the extent of disease can be accurately identified before treatment. In this thesis the addition of PET/CT to the standard staging of esophageal cancer patients has shown to prevent a futile attempt at curative esophagectomy by detecting interval metastasis, has made other diagnostic tests redundant (i.e. cervical ultrasonography), provides prognostic information, and improves detection of disease recurrence. At the same time, however, research in Chapter 4 demonstrated that staging of esophageal cancer patients in current clinical practice remains difficult and is highly inaccurate. As such, treatment recommendations that are made on the current available staging techniques will in part result in under- and over-treatment of patients. This emphasizes that improving outcomes for esophageal cancer patients will begin with improving and optimizing staging of esophageal cancer.

One technique that will improve current clinical staging in the near future includes MRI. Although MRI has not yet been integrated in the standard work-up of patients with esophageal cancer, MRI techniques are developing rapidly over time, enabling faster scans and improvement in image quality[1]. Consequently, the diagnostic and prognostic information of MRI will likely also improve and influence the accuracy of clinical decision making in the near future. Other imaging techniques that may improve staging include the integration of MRI with PET (PET/MRI), novel PET tracers, and use of radiomics[2,3]. However, given that individualized medicine will gradually become more defined, other than only imaging variables are required for staging. It seems inevitable that biomarkers and genomic assays will be incorporated in routine clinical practice over the next decades[4,5].

Nevertheless, different diagnostic tests often produce to various degrees the same information because they are all related to the same underlying disease. At the same time, each test may be more or less demanding for the patient, time-consuming, and/or expensive[6]. For clinical practice it is relevant to know which tests are redundant and which truly have added independent predictive or diagnostic value in the staging of esophageal cancer patients.

Accordingly, in future research novel staging techniques should demonstrate added value, beyond the test results readily available in clinical practice, for determining the presence or absence of a particular stage or subtype of disease. Furthermore, the burden that novel staging techniques may cause to our patients should always be considered before they are implemented in clinical practice (Chapter 10).

Detection of disease recurrence

One of the reasons that overall 5-year survival rates of patients with esophageal cancer who are treated with curative intent remains dismal, is that almost half of patients develop recurrent disease early after treatment[7]. Clinical decision-making with regard to selecting the appropriate treatment strategy for these patients will depend on the extent and location of the recurrent disease. The current thesis (Chapter 5) has shown that PET/CT is a valuable test for the detection of recurrent disease after treatment. The presumed benefit of routinely applying such test during follow-up is that early detection of recurrence allows for timely salvage therapy with improved quality of life and survival[8]. However, there is much room for improvement in this field. The present guidelines of Europe (ESMO) and North America (NCCN) do not support routine surveillance for the detection of recurrent disease, as the evidence that routine follow-up will lead to favorable results is yet too limited[9,10]. Indeed survival after recurrence, as shown in Chapter 6 and 7, is notoriously poor. Nevertheless, recent studies have shown that survival is significantly better in patients who receive salvage treatment for locoregional and distant recurrent disease[11,12]. This considerable improvement in survival by salvage treatment suggests that the early detection of recurrences is becoming more important.

One of the challenges of routine follow-up imaging, however, is that half of the patients – fortunately – do not develop disease recurrence after treatment[13,14]. Consequently, this group of the patients will not receive benefit of routine follow-up imaging. For this reason one could argue that surveillance should be tailored to each patients underlying risk of developing recurrence. This could prevent unnecessary imaging of low-risk patients and under-treatment of high-risk patients. However, in order to identify patients that may benefit of post-treatment follow-up imaging a tool is needed that can actually stratify patients in low-risk and high-risk groups. The externally validated nomogram for the prediction of recurrence free survival, as presented in Chapter 7, could be such tool in the design of a risk-stratified clinical follow-up strategy.

The current availability of a good diagnostic test for the detection of recurrent disease (Chapter 5), a validated stratification tool (Chapter 7) in combination with promising salvage treatment

strategies[11,12], suggests that a risk-based postoperative surveillance strategy could make sense in clinical practice. Therefore, research is needed to establish the level of costs and benefits afforded to patients as a result of such a strategy. Also there is a need for a better understanding of patients' preferences in this area. It is currently unclear to what extent patients wish to know their risk, especially when there may be few options to reduce these risk before they become an overt problem. Obviously, the development of novel treatment strategies for recurrent disease, in combination with improvement of prognostication by novel predictors, will contribute to the success of a risk-stratified follow-up strategy.

TREATMENT RESPONSE PREDICTION

Whereas esophagectomy has historically been the only treatment that could offer a reasonable chance for cure, patients can now be cured by multiple treatment strategies[9,10]. An important focus of research in the changing landscape of esophageal cancer treatment is to find powerful tools that can accurately determine the residual cancer status after neoadjuvant chemoradiotherapy. Accurate prediction of pathologic complete response before surgery would enable investigators to study the feasibility and outcome of an organ-preserving strategy after chemoradiotherapy. On the other hand, reliable identification of poor responders – that may benefit less or not at all from neoadjuvant chemoradiotherapy – early during treatment would enable investigators to study the feasibility and outcome of early modification or discontinuation of neoadjuvant chemoradiotherapy.

Unfortunately, most previously studied modalities – including endoscopic biopsy, endoscopic ultrasonography – yield unsatisfactory results for the evaluation of response to neoadjuvant chemoradiotherapy[15]. The promising results of two previously conducted prospective pilot studies by our research group encouraged us to further assess the utility of functional MRI (including diffusion-weighted MRI and dynamic contrast-enhanced MRI) for predicting pathologic response[16,17]. The findings of the prospective study described in Chapter 9 confirm that functional MRI yields predictive value in this setting. However, before this technique can be implemented in clinical practice, there are some challenges that need to be overcome. First, the prognostic value of functional MRI is reasonable, but not yet optimal. During the assessment of the functional MRI scans in our study, it became apparent that the quality of these scans for the purpose of response assessment deserve improvement. Furthermore, because in the course of our previous MRI study only one scan was conducted during neoadjuvant chemoradiotherapy, the optimal timing for response assessment using MRI remains unclear. Therefore, a follow-up study to improve MRI quality and assess the optimal

timing of functional MRI in the evaluation of treatment response is currently being conducted by our research group.

A second challenge lies in increasing the reproducibility and practical applicability of this technique in clinical practice. The current manual segmentation procedure of esophageal tumors for the quantitative analysis of functional MRI scans is considered a challenging and time-consuming process. Thus, the development of a fully-automated segmentation method for fast and reproducible functional MRI measurements will enhance practicability. With the emergence of machine learning (a field of science where computer algorithms are used to autonomously learn from data and information) the development of such methods is now possible[18].

In addition, the predictive ability of any standalone diagnostic modality will likely be insufficient to guide clinical decision making. In general, multimodal predictions produce more accurate results than any single modality alone[6]. Indeed, the current thesis shows that combining diffusion-weighted MRI, dynamic contrast-enhanced MRI, and PET/CT provide complementary information, resulting in higher predictive value for response assessment compared with single modalities. At the same time, several other novel modalities have emerged to predict response to treatment. The recent preSANO study has shown that the previously mentioned poor accuracy of endoscopic biopsy for response prediction can be improved by a more extensive and detailed sampling protocol accompanied with submucosal biopsies (i.e. bite-on-bite biopsies). Quantification of circulating tumor DNA represents another novel approach for cancer detection and disease burden quantification that has the potential to complement response prediction[18]. Although this phenomenon has been recognized for years, accurate techniques to detect circulating tumor DNA have only become available recently. With all these different techniques in mind, our research group recently designed a multi-center observational study that aims to develop a model that predicts the probability of pathologic complete response by combining diffusion-weighted MRI, dynamic contrast-enhanced MRI, PET-CT, bite-on-bite biopsies, and circulating tumor DNA acquired prior to, during and after administration of neoadjuvant chemoradiotherapy (ClinicalTrials.gov Identifier: NCT03474341).

Active surveillance vs. standard esophagectomy

Accurate prediction of patients with a pathologic complete response to neoadjuvant chemoradiotherapy would provide the rationale to analyze an organ-sparing active surveillance approach as, possibly, surgical resection of the esophagus in patients with no residual tumor

does not improve oncological outcome. In such treatment strategy, patients will enter a process of diagnostic re-evaluations after therapy[18]. In case locoregional recurrence is detected, in the absence of distant metastases, surgical therapy will be performed (i.e. salvage surgery).

An important caveat of an organ-sparing active surveillance approach will be the ability to timely detect locoregional recurrence, as this will influence the ability of surgeons to offer adequate salvage surgery. Undetected locoregional recurrences will progress to a non-resectable stage, even in the situation where there is no evidence of distant metastases[18]. In this context, death from local-regional disease should be – and will be by many – considered as the ultimate failure of therapy. Therefore, in the assessment of future active surveillance strategies a very important questions is how many patients will require salvage surgery, and how many will have missed an opportunity for cure because surgery was initially avoided. The latter will also be highly dependent on the accuracy of response prediction after neoadjuvant chemoradiotherapy. As such, there is currently some understandable controversy about trials that are assessing organ-sparing active surveillance strategies with insecure response prediction methods.

Regardless of the accuracy that future response prediction methods may bring us, the risk of locoregional recurrence during follow-up in an active surveillance approach will be significant, considering that even in patients with a pathologic complete response who are directly treated with surgery the risk of locoregional recurrence is approximately 15%[19]. Patients who eventually develop locoregional recurrence in an active surveillance program are confronted with limited curative treatment options, and should absolutely be reviewed by an esophageal surgeon to consider the option of salvage esophagectomy. Historically this has been considered a very challenging surgical procedure with a high-risk of postoperative morbidity[18]. With this in mind, the current seemingly inventible movement towards active surveillance approaches calls for specialized esophageal cancer surgeons that should preferably work in high-volume dedicated cancer centers[19].

In the setting of treatment response prediction, the obvious therapy for non-responders would be to perform surgery in order to achieve curative control of disease. Unfortunately, however, not all patients are amenable to achieve the excellent results owing to the radical surgery. In Chapter 6 we have shown that a group of patients has disease (i.e. occult micrometastsis) that is likely is to advanced to be optimally treated by esophagectomy. In case these patients could accurately be identified, an alternative less invasive strategy would be to delay esophagectomy and closely monitor patients for systemic disease. Yet, most physicians will – justly – find

it difficult to withhold surgery from a patient with a potential resectable tumor based on the currently available insecure risk prediction models for occult micrometastasis. As such, there is much to be gained by investing in novel research that aims to identify these patients.

Eventually, future improvement in prognostication will likely result in stratification of patients by risk of surgery balanced with chances of pathologic complete response and/or risk of occult distant metastases. Low-risk surgical patients with minimal chances of treatment response to neoadjuvant treatment and low-risk of occult distant metastasis should undergo planned surgical resection. In high-risk surgical patients with high-chances of tumor response to neoadjuvant treatment and/or high-risk of distant metastasis an active surveillance approach could be considered.

In the context of 'high-risk surgical patients', however, it is noteworthy that during the last decade multiple initiatives have been employed to reduce the morbidity associated with esophageal resections. The implementation of minimally invasive (robotic) esophagectomy is at an advanced stage, and has shown to reduce postoperative morbidity, shorten length of hospital stay and improve postoperative quality of life[20,21]. Furthermore, the increasing centralization of complex surgical procedures, such as esophagectomy, is improving the efficacy and reducing the morbidity of such procedures[22,23]. All these advances in surgical treatment will increase the percentage of patients who are eligible for surgical resection. Thus, in the decision to initiate either direct surgery or active surveillance, the invasiveness of esophagectomy should be evaluated and re-considered from time to time.

POSTOPERATIVE COMPLICATION MANAGEMENT

Complications after esophageal resection remain common and problematic with all their potential consequences[24]. The research in Chapters 11 and 12 demonstrates that pulmonary complications and anastomotic leakage have the greatest clinical impact on economic and health care outcomes after esophagectomy. These specific complications, therefore, should receive priority as targets of complication-related quality improvement initiatives. The approaches outlined below may be of use in reducing postoperative complications after esophagectomy.

Risk assessment

Accurate preoperative risk assessment of complications prior to surgery is an important first step in the process of reducing postoperative complications. It allows individual high-risk patients' perioperative care pathway to be optimized with the aim of reducing morbidity and

mortality. Furthermore, patients identified as poor surgical candidates could be considered for less invasive treatment strategies or surgical approaches (e.g. definitive chemoradiation or transhiatal esophagectomy). Chapters 13 through 18 made an important contribution, for that matter, by identifying novel perioperative factors (e.g. generalized calcification, intraoperative hemodynamic factors and radiation to the gastric fundus) to identify high-risk surgical patients. Of note, some of these Chapters were hypothesis generating or focused on single risk factors. As previously indicated, individual risk prediction when based on just one single factor is usually limited. Hence, an important next challenge in this field will be to combine all these novel prognostic factors within a prognostic model to improve patient selection based on their predicted individual risk of subsequent outcomes.

Radiation treatment planning

As shown in chapter 16 and 17, the current radiotherapy of esophageal tumors is not without adverse effects due to dose delivery to organs surrounding the tumor (e.g. heart, lungs, fundus). Radiation induced adverse events (e.g. radiation pneumonitis, anastomotic leakage, and ischemic heart disease) can directly be related to the radiation dose delivered to these tissues[25–27]. The recent introduction of improved radiotherapy techniques such as intensity modulated radiation therapy (IMRT) have already resulted in a reasonable reduction of radiation dose to organs at risk[28]. Yet, there is still room for improvement. The recent development of the MRI Linac (MRL) system allows for precise real time and on-line MRI guidance of external beam radiation[28]. By tracking both the tumor and organs at risk during treatment tighter irradiation margins and improved sparing of organs at risk can be applied. This will likely result in a reduction of short-term and long-term toxicity. Proton beam radiotherapy is another technologically advanced radiation technique of growing interest. The distinct physical characteristics of charged particles in proton beam radiotherapy have the potential to improve target coverage and reduce dose to organs at risk when compared with conventional photon therapy[29]. Furthermore, the higher relative biological effectiveness of protons might have the potential to further improve response to treatment[30]. Despite theoretical superiority, the clinical advantage of MRL and proton beam based radiotherapy in patients with esophageal cancer remains to be determined.

Surgical techniques

Recently, robot-assisted minimally invasive esophagectomy (RAMIE) was introduced with the aim to reduce the relatively high morbidity associated with esophagectomy, while enabling a safe and radical oncologic resection[31,32]. The current benefit of robotic surgery lies in its ability of easy manipulation and high three-dimensional quality visualization

compared to the conventional minimally invasive approach. These adjustments increase accuracy and enable surgeons to perform more complex dissections, such as a meticulous mediastinal lymphadenectomy, or a hand-sewn intrathoracic anastomosis in the context of esophagectomy[33]. Yet, robotics for surgery will soon bring more to the table than just improving manipulation and visualization. Robotic systems allow for the collection of data and videos that are generated during surgical procedures. Analyzing all these data from massive databases with machine-learning algorithms may enable robotic systems to aid surgeons in improving their surgical procedures. For example, when a sequence of specific surgical techniques can be correlated with an outcome (e.g. a complication or irradical resection), they can inform the surgeon on their technique and provide suggestions for improvement. With this in mind, the combination of robotic systems and machine learning has the potential bring preciseness and efficacy of surgery to a new level. Although this exciting development sounds promising, evidence of these potential benefits have yet to be generated.

LAST REMARKS

The aim of this thesis was to reduce treatment related morbidity and ensure maximal benefit of treatment by optimizing patient selection and improve the use of existing therapies for patients with esophageal cancer. In order to achieve this aim many chapters focused on the prediction or assessment of a particular outcome (e.g. interval metastasis, tumor response, anastomotic leakage), and discussed the consequences of being able to predict or identify such a 'single' outcome. Yet, physicians know that in order to individualize treatment multiple probabilities associated with different outcomes for an individual have to be considered simultaneously. As such, the multitude of available prediction models for separate outcomes makes treatment-decision making more complex. On the one hand, this calls for single-organ cancer specialists who can oversee all different options and consequences for individual patients. On the other hand, if we really want to support physicians in treating their patients it is desirable to generate models that evaluate different diagnostic and treatment strategies, and their effect on the probability of different outcomes simultaneously. Such models can then be used to help decide on the optimal overall treatment strategy that incorporate the potential benefits of cancer treatment (i.e. disease free survival), the risk of toxicity, and potential gain or loss of quality of life. Nevertheless, the research in this thesis contributes to this development by pointing towards the use of specific diagnostic tools, novel predictors and models for individual risk estimation, and remaining gaps in esophageal cancer research.

CONCLUSIONS

Part 1. Staging

Chapter 2 Cervical ultrasonography has no additional diagnostic value to a negative PET/CT for the detection of cervical lymph node metastases in patients with newly diagnosed esophageal cancer

Chapter 3 A restaging PET/CT after neoadjuvant chemoradiotherapy can prevent a futile attempt at curative esophagectomy in 8% of patients by detecting interval metastasis

Chapter 4 Compared to surgery alone, neoadjuvant chemoradiotherapy followed by surgery is associated with higher radical resection rates and improves overall survival for patients with clinical T2N0 esophageal cancer

Chapter 5 PET/CT is a reliable imaging modality with a very high sensitivity and moderate specificity for the detection of recurrent esophageal cancer after treatment with curative intent

Chapter 6 A nomogram based on gender, poor histologic grade, signet ring cell adenocarcinoma, clinical nodal stage, and baseline SUV_{max} is predictive for early disease recurrence after neoadjuvant chemoradiotherapy followed by surgery for patients with esophageal cancer

Chapter 7 A nomogram based on clinical nodal stage, pathological tumour stage and number of positive lymph nodes in the resection specimen can accurately predict overall survival after neoadjuvant chemoradiotherapy followed by surgery for patients with esophageal cancer

Part 2. Treatment response prediction

Chapter 8 Tumor cellularity measured by DW-MRI and tumor metabolism measured by PET/CT are independent cellular phenomena in newly diagnosed esophageal cancer, and may therefore have complementary value in the prediction of treatment response

Chapter 9 DW-MRI and DCE-MRI provide complementary information for the prediction of treatment response to neoadjuvant chemoradiotherapy in esophageal cancer

Chapter 10 Repeated imaging with both MRI and PET/CT is generally well-tolerated by patients for the assessment of response to neoadjuvant chemoradiotherapy for esophageal cancer

Part 3. Postoperative complication management

Chapter 11 Complications and severity of complications after esophageal surgery are associated with a substantial increase in healthcare costs

Chapter 12 Compared to other complications, anastomotic leakage and pulmonary complications have the greatest overall impact on postoperative mortality, prolonged hospitalization, reoperations, and hospital readmission after esophagectomy for cancer

Chapter 13 Atherosclerotic calcification of the aorta, measured on a preoperative CT, is an independent risk factor for leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy

Chapter 14 Atherosclerotic calcification of the entire cardiovascular system, measured on a preoperative CT, is a strong indicator for the risk of anastomotic leakage after Mckeown esophagectomy

Chapter 15 A low minimum intraoperative pH is associated with an increased risk of anastomotic leakage, whereas a low average mean arterial pressure is associated with an increased risk of pneumonia.

Chapter 16 Compared to perioperative chemotherapy, neoadjuvant chemoradiotherapy achieves higher pathologic response rates and a lower risk of locoregional disease progression, without increasing postoperative complications.

Chapter 17 High radiation dose levels to the gastric fundus are associated with an increased risk of anastomotic leakage after esophagectomy.

Chapter 18 Compared to a cervical esophagogastric anastomosis, an intrathoracic anastomosis is associated with a lower anastomotic leak rate, lower rate of recurrent nerve paresis and a shorter hospital stay

Chapter 19 The presence of mediastinal fluid, mediastinal air, esophagogastric wall discontinuity and a fistula on a postoperative CT scan are suggestive for the presence of an anastomotic leak

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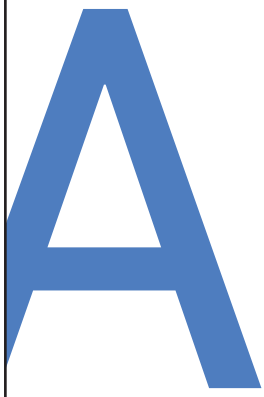
Appendices



SUMMARY IN DUTCH – NEDERLANDSE SAMENVATTING

De incidentie van het oesophaguscarcinoom is de afgelopen decennia gestegen, waardoor het oesophaguscarcinoom een toenemend gezondheidsprobleem vormt. Ruim de helft van de patiënten met een oesophaguscarcinoom komt bij de eerste klinische presentatie niet in aanmerking voor een curatieve behandeling door de aanwezigheid van afstandsmetastasen. Neoadjuvante chemoradiotherapie in combinatie met chirurgische resectie van de oesophagus is in het algemeen de behandeling van voorkeur met curatieve intentie bij patiënten zonder afstandsmetastasen. Ondanks recente vooruitgang in de beschikbare diagnostiek en behandelmogelijkheden, bestaat er een aanzienlijk risico om te komen te overlijden na een in opzet curatieve behandeling (5-jaarsoverleving ≈ 50%). Dit is onder andere toe te schrijven aan het feit dat groot deel van de patiënten niet voldoende reageert op de huidige beschikbare behandelingen, terwijl deze wel beduidende risico's op morbiditeit en zelfs sterfte met zich meebrengen. Om deze teleurstellende behandelingsresultaten te verbeteren is het van belang om aan de hand van individuele patiënt en individuele tumor karakteristieken de behandeling met het best mogelijke resultaat te selecteren. De onderzoeken in dit proefschrift hadden als doel om patiëntselectie voor een eventuele oesophagusresectie te optimaliseren. Om dit doel te bereiken werden in dit proefschrift verbeteringen voorgesteld voor de diagnostiek en stadiëring van de ziekte (deel 1), voorspelling van de respons op neoadjuvante chemoradiotherapie (deel 2) en preventie en detectie van postoperatieve complicaties (deel 3). In het huidige hoofdstuk worden de onderzoeken die in dit proefschrift zijn gepresenteerd samengevat.

DEEL 1. STADIËRING

Het stadium waarin het oesophaguscarcinoom zich bevindt is één van de belangrijkste factoren die de prognose van patiënten bepaalt en heeft daardoor veel invloed op de behandelingskeuze. Het stadium wordt met name bepaald door de grootte van de primaire tumor en de aan- of afwezigheid van lymfeklier- en afstandsmetastasen. In deel 1 van dit proefschrift werd de huidige stadiëring van het oesophaguscarcinoom onderzocht om daarmee accuraat de optimale behandeling voor de individuele patiënt te selecteren.

Hoofdstuk 2. Beeldvorming van cervicale lymfklieren

Door de toevoeging van PET/CT aan de standaard diagnostiek van het oesophaguscarcinoom is de diagnostische accuratesse van de stadiering toegenomen. In dit onderzoek werd de toegevoegde waarde van cervicale ultrasonografie tijdens de initiële stadiëring voor het diagnosticeren van cervicale lymfekliermetastasen van het oesophaguscarcinoom geëvalueerd. Er werd geen aanvullende diagnostische waarde van cervicale ultrasonografie gevonden ten opzichte van de PET/CT onderzoeken in het detecteren van cervicale lymfekliermetastasen.

Deze bevindingen tonen aan dat het routinematig uitvoeren van cervicale ultrasonografie tijdens de initiële stadiëring achterwege kan worden gelaten.

Hoofdstuk 3. Detectie van interval metastasen

Het detecteren van interval metastasen na de neoadjuvante chemoradiotherapie is cruciaal voor het selecteren van patiënten die baat zullen hebben van een oesophagusresectie. De huidige Nederlandse richtlijn adviseert niet om routinematig een PET/CT te verrichten om deze interval metastasen op te sporen. In dit onderzoek werd aangetoond dat een PET/CT na neoadjuvante chemoradiotherapie in 8% van de patiënten interval metastasen detecteert en zodoende een onnodige oesophagusresectie kan voorkomen. In multivariabele analyse werd aangetoond dat de lengte van de tumor, het klinisch N-stadium, de baseline SUV_{max} waarde, en het plaveiselcelcarcinoom risicofactoren zijn voor het ontstaan van interval metastasen. Aan de hand van deze factoren werd een predictiescore ontwikkeld die artsen in staat stelt om aanvullend PET/CT onderzoek na neoadjuvante chemoradiotherapie te beperken tot hoog risico patiënten.

Hoofdstuk 4. Stadiëring en behandeling van klinische T2N0 tumoren

Neoadjuvante chemoradiotherapie heeft een vaste plaats gekregen binnen de curatieve behandeling van het potentieel resectabel oesophaguscarcinoom. De rol van chemoradiotherapie bij patiënten met een klinisch gestadieerd T2N0 oesophaguscarcinoom is echter onbeslist. In dit landelijke cohort onderzoek werd de huidige klinische stadiëring en waarde van neoadjuvante chemoradiotherapie in patiënten met T2N0 tumoren geëvalueerd. Hierbij werden patiënten met neoadjuvante chemoradiotherapie gevolgd door een oesophagusresectie vergeleken met patiënten die enkel een oesophagusresectie ondergingen. Neoadjuvante chemoradiotherapie resulteerde in een significant hogere kans op radicale chirurgische resectie en een betere overleving. Klinische onderstadiëring werd in ruim 60% van de patiënten geobserveerd. Deze resultaten geven aan dat – totdat de huidige klinische stadiëring aanzienlijk verbetert – neoadjuvante chemoradiotherapie de voorkeursbehandeling is voor patiënten met een klinisch gestadieerd T2N0 oesophaguscarcinoom.

Hoofdstuk 5. Detectie van het recidief oesophaguscarcinoom middels PET/CT

Vanwege beperkte therapeutische opties voor patiënten met een recidief oesophaguscarcinoom na initiële curatieve behandeling wordt in de klinische praktijk op dit moment niet actief gescreend op deze zieke. Echter wordt in de huidige internationale literatuur steeds vaker geopteerd voor agressievere behandeling van deze ziekte, waardoor het vroegtijdig diagnosticeren van deze recidieven steeds meer van belang wordt. In deze meta-analyse werd

aangetoond dat PET/CT een betrouwbare diagnostische test is, met een hoge sensitiviteit en gematigde specificiteit, voor de detectie van het recidief oesophaguscarcinoom na een in opzet curatieve behandeling. Door het hoge aantal vals-positieven blijft histopathologische bevestiging van op PET/CT verdachte laesies noodzakelijk. Toekomstig onderzoek moet aantonen of vroege detectie van een recidief, samen met agressieve therapeutische strategieën, de overleving en kwaliteit van leven van deze patiënten zal verbeteren.

Hoofdstuk 6. Predictie van een vroeg recidief na een oesophagusresectie

Bij patiënten die snel een recidief ontwikkelen na neoadjuvante chemoradiotherapie gevolgd door een oesophagusresectie, weegt het voordeel van chirurgie mogelijk niet op tegen de nadelen. Om deze groep patiënten voorafgaand aan de behandeling te kunnen identificeren, werd in dit onderzoek een predictie score voor 1-jaars ziekte vrije overleving ontwikkeld. De 1-jaar ziekte vrije overleving werd het beste voorspeld door een combinatie van de volgende vijf factoren: geslacht, histologische gradering, zegelringcel differentiatie, het klinisch N-stadium en de baseline SUV_{max} waarde. Het in dit onderzoek ontwikkelde scoresysteem stelt artsen in staat om vóór de chirurgie een geïndividualiseerde voorspelling te genereren over het risico op een vroeg recidief. Als zodanig kan het scoresysteem de klinische besluitvorming ondersteunen. Externe validatie en verbetering van het scoresysteem met nieuwe voorspellers is noodzakelijk voordat deze veilig in de klinische praktijk kan worden geïmplementeerd.

Hoofdstuk 7. Predictie van overleving na oesophagusresectie

Nauwkeurige voorspelling van overleving na een oesophagusresectie kan leiden tot patiënt specifieke follow-up en vroege initiatie van adjuvante behandelstrategieën. Het doel van dit onderzoek was het extern valideren van een nomogram dat de overleving voorspelt – op basis van cN, pT en pN-status – van patiënten met een oesophaguscarcinoom na behandeling middels neoadjuvante chemoradiotherapie gevolgd door een oesophagusresectie. Voor externe validatie van dit nomogram werd een internationaal multicenter cohort onderzoek opgezet met patiënten uit het Universitair Medisch Centrum Utrecht, het MD Anderson Cancer Center Houston en de Mayo Clinics Rochester. Het discriminerend vermogen van het nomogram was redelijk – vergelijkbaar met de initiële studie – en de kalibratie van het nomogram bleek nauwkeurig bij visuele beoordeling. Deze resultaten bevestigen dat voor patiënten met een oesophaguscarcinoom die behandeld worden middels neoadjuvante chemoradiotherapie gevolgd door een oesophagusresectie de overleving redelijk kan worden voorspeld met behulp van een nomogram op basis van cN, pT en pN-status. Identificatie van nieuwe prognostische factoren is noodzakelijk om het huidige nomogram te optimaliseren.

DEEL 2. PREDICTIE VAN RESPONS OP CHEMORADIOTHERAPIE

Nauwkeurige voorspelling van pathologisch complete respons van de tumor op chemoradiotherapie voorafgaand aan een oesophagusresectie zou onderzoekers in staat stellen om de haalbaarheid en uitkomsten van een orgaansparende behandelstrategie – waarbij oesophagusresectie achterwege gelaten wordt – te onderzoeken. De huidige beschikbare diagnostische onderzoeken zijn niet nauwkeurig genoeg om een dergelijke behandelstrategie veilig te implementeren. Het doel van deel 2 van dit proefschrift was het voorspellen van de respons op de neoadjuvante behandeling.

Hoofdstuk 8. Correlatie tussen diffusie-gewogen MRI en PET/CT

De 'apparent diffusion coefficient' (ADC), verkregen met behulp van diffusie-gewogen MRI, en de 'standardized uptake value' (SUV), verkregen middels PET/CT, zijn bekende prognostische parameters in oncologische beeldvorming. Het is echter onduidelijk of deze twee parameters complementaire prognostische informatie bevatten. In dit prospectieve onderzoek werd bij patiënten met een oesophaguscarcinoom de correlatie tussen tumor ADC en SUV waarden beoordeeld. Verwaarloosbare, niet-significante, correlaties werden gevonden tussen deze twee parameters. Dit toont aan dat tumor ADC en SUV waarden onafhankelijk zijn, en waarschijnlijk complementaire waarde hebben voor het voorspellen van de respons op neoadjuvante behandeling voor het oesophaguscarcinoom.

Hoofdstuk 9. Predictie van tumor respons middels MRI

Twee recente pilotstudies van onze onderzoeksgroep hebben laten zien dat veranderingen in de tumor, die worden waargenomen middels diffusie-gewogen MRI en dynamische contrast-versterkte MRI, het effect van neoadjuvante chemoradiotherapie op het oesophaguscarcinoom kunnen voorspellen. In hoofdstuk 9 werd onderzocht of het combineren van beide MRI technieken het voorspellen van de respons op neoadjuvante chemoradiotherapie kan verbeteren. Het combineren van diffusie-gewogen MRI en dynamische contrast-versterkte MRI resulteerde in een betere voorspelling van de respons op behandeling. Vanwege matige MRI kwaliteit werd een aanzienlijk aantal patiënten uit deze analyse geëxcludeerd. Derhalve heeft onze onderzoeksgroep recent geïnvesteerd in het verbeteren van de MRI kwaliteit en in een multicenter onderzoek om de resultaten van het huidige onderzoek te valideren.

Hoofdstuk 10. Patiëntperspectieven op herhaalde MRI en PET/CT onderzoeken

Vanwege de toename in het aantal diagnostische onderzoeken, onder andere voor de predictie van tumor respons, verdient de fysieke en mentale belasting van deze onderzoeken voor de patiënt extra aandacht. In dit onderzoek werd de ervaren belasting van herhaalde MRI

en PET/CT onderzoeken tijdens de neoadjuvante behandeling geëvalueerd met behulp van vragenlijsten. De gerapporteerde incidentie van ongemak, pijn, angst en/of schaamte tijdens de onderzoeken was laag. In het algemeen lijken patiënten zowel MRI als PET/CT goed te verdragen en als zodanig kunnen beiden worden gebruikt voor de predictie van respons op neoadjuvante chemoradiotherapie.

DEEL 3. POSTOPERATIEVE COMPLICATIES

Oesophagusresectie is een essentieel onderdeel van de curatieve behandeling bij patiënten met een oesophaguscarcinoom. Door de nauwe anatomische relatie van de oesophagus met omliggende vitale organen, zoals het hart en de longen, gaat deze procedure gepaard met een hoog risico op postoperatieve complicaties. De gerapporteerde frequentie van postoperatieve complicaties na deze procedure varieert tussen de 40% en 60%, waarbij pneumonie en naadlekkage de meest voorkomende complicaties zijn. In deel 3 van dit proefschrift werden oorzaken, risicofactoren en de diagnostiek van postoperatieve complicaties na oesophagusresectie onderzocht.

Hoofdstuk 11. Kosten van postoperatieve complicaties

Onderzoek naar de economische impact van postoperatieve complicaties kan bijdragen aan een efficiëntere inzet van financiële middelen bij patiënten met een oesophaguscarcinoom. In dit onderzoek naar klinische- en financiële resultaten van oesophagusresecties in het Universitair Medisch Centrum Utrecht, werd gevonden dat de gemiddelde kosten voor één oesophagusresectie €37.581 bedragen. Gemiddelde kosten na een ongecompliceerd beloop waren €23.476 en na ernstige complicaties €59.167. Ernstige complicaties werden in 29% van de patiënten geobserveerd en de kosten van ernstige complicaties besloegen 40% van de totale zorgkosten die gemoeid zijn met een oesophagusresectie. De resultaten van dit onderzoek geven aan dat implementatie van preventieve maatregelen voor postoperatieve complicaties niet alleen zullen bijdragen aan een afname in morbiditeit maar ook in zorgkosten.

Hoofdstuk 12. Klinische gevolgen van postoperatieve complicaties

Om beschikbare financiële middelen zo efficiënt mogelijk in te zetten, moeten initiatieven die de zorg rond oesophagusresecties willen verbeteren zich richten op de complicaties die de meeste impact hebben op klinische uitkomsten na oesophagusresectie. Sinds 2011 worden alle postoperatieve complicaties en klinische uitkomsten na oesophagusresecties in Nederland geregistreerd. In hoofdstuk 12 werd aangetoond dat naadlekkage en pulmonale complicaties de belangrijkste veroorzakers waren van postoperatieve mortaliteit, langdurige ziekenhuisopname, heroperaties en heropnames. Derhalve zullen initiatieven die met succes de

frequentie van deze complicaties verminderen, de grootste bijdrage leveren aan de verbetering van klinische uitkomsten na oesophagusresecties.

Hoofdstuk 13. Aorta calcificaties en naadlekkage

Eerder heeft onze onderzoeksgroep aangetoond dat atherosclerose van de thoracale aorta geassocieerd is met naadlekkage na een oesophagusresectie. Om de klinische toepassing van deze nieuwe risicofactor te evalueren is externe validatie noodzakelijk. In dit onderzoek werd in een cohort van patiënten uit Almelo en Eindhoven bevestigd dat atherosclerose van de thoracale aorta een onafhankelijke risicofactor is voor naadlekkage. Deze risicofactor kan worden gebruikt bij patiëntselectie voor interventies die als doel hebben de conditie van de anastomose te optimaliseren.

Hoofdstuk 14. Gegeneraliseerde atherosclerose en naadlekkage

Zoals vermeld in de samenvatting van het vorige hoofdstuk is aangetoond dat atherosclerose van de thoracale aorta geassocieerd is met het optreden van naadlekkage na een oesophagusresectie. Het is echter tot dusver niet bekend of deze associatie alleen veroorzaakt wordt door beperkingen in de locoregionale bloedvoorziening (calcificaties in de thoracale aorta), of ook door gegeneraliseerde vaatziekte (calcificaties elders). In dit onderzoek werd aangetoond dat calcificaties in de supra-aortale en coronaire arteriën een hogere voorspellende waarde hebben voor naadlekkage dan calcificaties in de thoracale aorta. Deze bevindingen kunnen gebruikt worden om hoog risicopatiënten te identificeren.

Hoofdstuk 15. Perioperatieve risicofactoren voor naadlekkage en pneumonie

Het identificeren van hemodynamische en respiratoire factoren die van invloed zijn op het optreden van naadlekkage en pneumonie kan bijdragen aan het ontwikkelen van interventies om deze complicaties te voorkomen. In dit onderzoek werden bij opeenvolgende patiënten die een electieve oesophagusresectie ondergingen uitgebreide metingen van hemodynamische en respiratoire factoren verricht tijdens en vroeg na de operatie. Een laag intraoperatief arterieel pH (<7,25) was significant geassocieerd met naadlekkage, terwijl een lagere gemiddelde 'mean arterial pressure' (<88 mmHg) in de eerste 12 uur na operatie geassocieerd was met pneumonie. Deze parameters laten een toestand van cardiorespiratoire instabiliteit zien. Uit toekomstig onderzoek moet blijken wat het effect is van hemodynamische en respiratoire interventies om deze instabiliteit te voorkomen.

Hoofdstuk 16. Perioperatieve chemotherapie versus chemoradiotherapie

Recent onderzoek heeft aangetoond dat behandeling met neoadjuvante chemoradiotherapie of perioperatieve chemotherapie zorgt voor een toename in de overleving van patiënten met een resectabel adenocarcinoom van de oesophagus. Echter, na de introductie van neoadjuvante chemoradiotherapie in de klinische praktijk rapporteerden meerdere ziekenhuizen een toename in postoperatieve complicaties. Momenteel is het onduidelijk welke behandeling de voorkeur verdient in deze groep patiënten. In dit onderzoek werden beide behandelingsstrategieën met elkaar vergeleken in een groep patiënten uit het Universitair Medisch Centrum Utrecht ten aanzien van bijwerkingen, postoperatieve complicaties en langere termijn overleving. Beide strategieën waren geassocieerd met bijwerkingen, waarbij het risico op postoperatieve complicaties gelijk was tussen beide groepen. Hoewel chemoradiotherapie geassocieerd was met een hogere pathologisch complete respons van de tumor, vertaalde dit resultaat zich niet in een betere algehele overleving.

Hoofdstuk 17. Bestralingsdosis op de maagfundus en naadlekkage

Zoals vermeld in de samenvatting van het vorige hoofdstuk zijn er zorgen over een mogelijke toename in postoperatieve complicaties door het gebruik van neoadjuvante chemoradiotherapie. In recente literatuur is beschreven dat de bestralingsdosis op het deel van de maag waar later de anastomose van wordt geconstrueerd, de maagfundus, tijdens de neoadjuvante chemoradiotherapie een potentiele risicofactor is voor het ontwikkelen van naadlekkage. In dit onderzoek werd bevestigd dat een hogere stralingsdosis op de maagfundus het risico op naadlekkage verhoogt. Deze bevinding is belangrijk voor de klinische praktijk omdat het suggereert dat de stralingsdosis op de maagfundus tijdens het plannen van de neoadjuvante chemoradiotherapie moet worden geminimaliseerd.

Hoofdstuk 18. Cervicale versus intrathoracale anastomose

Het is momenteel onduidelijk wat de optimale locatie van de anastomose is na een oesophagusresectie. De incidentie van naadlekkage en overige morbiditeit werd vergeleken tussen patiënten met een cervicale anastomose en een intrathoracale anastomose. Propensity score matching werd gebruikt om te corrigeren voor potentiële confounders. Een intrathoracale anastomose was geassocieerd met minder naadlekkage, minder stembandparese en een kortere mediane ziekenhuisopnameduur.

Hoofdstuk 19. Diagnose van naadlekkage middels een CT

Vroegtijdige detectie van naadlekkage is van essentieel belang om de postoperatieve morbiditeit en mortaliteit na oesophagusresecties te beperken. Momenteel zijn er geen

duidelijke, objectieve criteria voor het detecteren van naadlekkage met CT. In dit onderzoek werd aangetoond dat vocht in het mediastinum, lucht in het mediastinum, wanddiscontinuïteit van de buismaag en/of een fistel op een postoperatieve CT onafhankelijk geassocieerd zijn met de aanwezigheid van naadlekkage. Aan de hand van deze radiologische bevindingen werd een diagnostische score ontwikkeld voor het vaststellen van naadlekkage. In vergelijking met de conventionele huidige radiologische beoordeling, heeft de nieuwe diagnostische score een beter detecterend vermogen.

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2018

1. **Goense L**, Meziani J, Ruurda JP, van Hillegersberg R. Impact of postoperative complications on outcomes after oesophagectomy for cancer. Br J Surg. 2018. [In Press]

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A

CURRICULUM VITAE

Lucas Goense was born on the 2nd of April 1989 in Wageningen, The Netherlands. After graduating from bilingual secondary school at the Marnix College in Ede in 2007, he attended medical school at Utrecht University. During his studies he was an active member of several student associations, took part in the organizing committee of the 'Medical Interfaculty Conference' for medical students in Utrecht in 2012, and he was member of the medical students' representative council. He performed his final internship and research project at the Department of Surgical Oncology of the University Medical Center Utrecht.

Following graduation as a medical doctor in 2014, he started his interdisciplinary PhD research on the perioperative management of esophageal cancer at the Departments of Surgery and Radiation Oncology of the University Medical Center Utrecht, under supervision of Prof. dr. R. van Hillegersberg, Prof. dr. C.H.J. Terhaard, Dr. G.J. Meijer, and Dr. J.P. Ruurda. In 2017, during his PhD research he was awarded the René Vogels Stipendium that enabled him to perform a research fellowship at The University of Texas MD Anderson Cancer Center, Houston, USA, to collaborate with Dr. S.H. Lin. In that same year he received a postgraduate Master of Science degree in Epidemiology at Utrecht University. In addition, he presented several of his papers at national and international conferences. In 2018 he started his clinical career as a resident not in training at the Department of Surgery of the St. Antonius Hospital in Nieuwegein.

Lucas currently lives in Amsterdam together with Nathalie Claessens. Outside of work, he enjoys speed skating, road cycling, reading, and spending time with family and friends.