Multimodality treatment and response assessment in esophageal cancer

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PhD thesis, Utrecht University, the Netherlands

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Multimodale behandeling en evaluatie van het effect van behandeling in patiënten met slokdarmkanker

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 12 november 2020 des middags te 2.30 uur

door

Alicia Sabine Borggreve

geboren op 8 maart 1992
te Venray

Contents

Part III. Surgical treatment

Part IV. Summary and general discussion

Appendices

General introduction and thesis outline

Esophageal cancer

Esophageal cancer is the seventh most common type of cancer and the sixth leading cause of cancer-related deaths worldwide, with over half a million new cases and deaths yearly.[1] At time of diagnosis, at least half of patients already suffer from locally unresectable or metastatic disease, leaving a minority eligible for treatment with curative intent.[2] Although primary surgical resection of the esophagus with en-bloc lymphadenectomy has long been the standard for treatment with curative intent of locally advanced esophageal cancer (i.e., cT1N+M0 or cT2-4aN0-3M0), the addition of neoadjuvant therapy (i.e. neoadjuvant chemoradiotherapy or perioperative chemotherapy) has increased 5-year survival rates to 40-50%.[3–7] As clear evidence for clinical superiority of either neoadjuvant chemoradiotherapy or perioperative chemotherapy is lacking, considerable variation exists regarding the exact regimens that are applied worldwide. Nonetheless, the global consensus is that multimodality treatment, which implies neoadjuvant chemoradiotherapy or perioperative chemotherapy in combination with esophageal resection, should be the standard of care for locally advanced esophageal cancer.[8]

While the implementation of neoadjuvant chemoradiotherapy and perioperative chemotherapy has improved survival for patients undergoing curative treatment for esophageal cancer, all therapies carry their own efficacy and toxicity profile. As these may depend on specific patient characteristics and tumor biology, it would be beneficial to move towards tailor-made strategies for the individual patient. As such, patients who do not benefit from neoadjuvant therapy could go directly to surgery – avoiding additional toxicity –, whereas patients without residual cancer after neoadjuvant therapy (i.e., complete responders) may follow an active surveillance policy. In this light, the research presented in this thesis aims at improvements in neoadjuvant chemoradiotherapy (**part I**), treatment response assessment (**part II**) and surgical treatment (**part III**) in patients with esophageal cancer.

Multimodality treatment

As previously described, multimodality treatment has become standard of care for patients with locally advanced esophageal cancer. Just after the turn of the last century, the MAGIC study[6] and French FNCLCC/FFCD 9703 study[9] were the first to report an overall survival benefit for perioperative chemotherapy in patients with lower esophageal, gastroesophageal junction and gastric adenocarcinoma. Subsequently, the Dutch randomized controlled CROSS trial combined chemotherapy with 41.4 Gy radiation therapy and demonstrated a 14% increase in 5-year overall survival for patients with either squamous cell carcinoma or adenocarcinoma treated with neoadjuvant chemoradiotherapy followed by surgery

compared to surgery alone.[5,10] These results led to the widespread application of neoadjuvant chemoradiotherapy for locally advanced esophageal cancer in mainland Europe. However, considerable heterogeneity remains in neoadjuvant chemoradiotherapy regimens applied in worldwide clinical practice, with radiation dosages ranging from 35.0 to 50.4 Gy, accompanied by various chemotherapy regimens.[5,11–14]

While determining the optimal treatment, it is of interest to optimize response rates while balancing the toxicities associated with neoadjuvant therapy.[5,15,16] Treatment intensification with higher neoadjuvant radiation dosages might increase pathological response rates, but could also cause more adverse events. These adverse events might negatively influence a patient's quality of life, and might also prevent patients from proceeding to surgery. Toxic effects of neoadjuvant chemoradiotherapy might be reduced by better visualization of the target volume during administration of radiotherapy. Due to the presence of positioning uncertainties and respiratory motion, substantial margins are currently applied for radiotherapy. However, smaller margins might result in a reduced radiation dose to the surrounding healthy tissues, and could thereby reduce short- and long-term complications.[17] Also, smaller dose plans might enable increased dosage to the tumor, while maintaining the dose constraints for healthy tissues that are currently used.

For the abovementioned reasoning, **part I** of this thesis will focus on optimizing response rates of neoadjuvant chemoradiotherapy while balancing the toxicities, as well as providing insight in the consequences of toxicities of neoadjuvant chemoradiotherapy for the patient.

Treatment response assessment

The improvement in survival after multimodality therapy is largely dependent on tumor response to neoadjuvant chemoradiotherapy, which can be assessed by histological examination of the resected esophagus. Nearly one third of all esophageal cancer patients (29%) who underwent neoadjuvant chemoradiotherapy have no residual viable tumor cells at the primary tumor site upon histopathological evaluation of the resection specimen, referred to as pathologic complete response.[5] Patients with a pathologic complete response have a favorable prognosis compared to other subgroups, with a lower risk of developing a locoregional recurrence and an increased survival.[10,18–21] It has been argued that in patients who achieve a pathologic complete response, surgery may be omitted without substantially reducing survival. In fact, as an esophagectomy is associated with substantial morbidity, mortality (up to 3-5%) and impaired quality of life[22–26], it can be speculated that surgery may only have a detrimental effect on these patients. Consequently, proper identification of pathologic complete responders prior to surgery could yield an organ-preserving regimen avoiding esophagectomy and its postoperative complications.

Conversely, patients with a poor response to neoadjuvant chemoradiotherapy are likely to benefit less or not at all from neoadjuvant chemoradiotherapy, but are exposed to its side-effects. A reliable identification of poor responders during neoadjuvant chemoradiotherapy may thus also be beneficial, as ineffective therapy could be stopped or alternative treatment strategies could be explored.

Several studies have been initiated to preoperatively evaluate tumor response to neoadjuvant chemoradiotherapy in order to individualize treatment strategies. Diagnostic strategies such as endoscopic biopsies and/or endoscopic ultrasonography (EUS),[27] ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET/CT),[28,29] diffusion weighted (DW)[30–33] and dynamic contrast-enhanced (DCE)[34] magnetic resonance imaging (MRI) have demonstrated their potential for response prediction, but do not yet individually fulfill the requirements to justify changes in treatment decision-making. As such, studies researching the performance of a multimodality imaging approach for response assessment are the main focus of this thesis and are presented in **part II**.

Surgical treatment

Following neoadjuvant chemoradiotherapy, esophagectomy with lymphadenectomy is recommended for all patients who did not progress during neoadjuvant therapy and are considered fit for surgery.[4] Esophagectomy is a highly complex surgical procedure that is associated with higher local control rates compared to chemoradiotherapy alone, at the cost of relatively high morbidity rates.[3] As such, accurate patient selection for surgery is necessary and does not only depend on tumor and treatment response characteristics, but also on assessment of comorbidities, a patients' nutritional status and cardiopulmonary function. A substantial percentage of patients diagnosed with esophageal cancer has a history of hypertension, congestive heart failure, smoking, and diabetes mellitus.[24] These comorbidities are well known risk factors for several postoperative complications and might also influence whether a patient proceeds to surgery after neoadjuvant therapy.

Next to patient-related risk factors, improved diagnostic procedures may further facilitate improved patient selection. Since all patients undergo extensive preoperative staging, obtaining objective information on for instance a patient's vascular status does not require any additional tests or imaging. With these extensive possibilities, a holistic view of the patient can be obtained, providing insight in the risk of postoperative complications. Preoperative identification of patients at higher surgical risk may provide opportunities to modify these risk factors or more fully optimize patients' conditions before surgery.

Part III of this thesis will address the surgical treatment of esophageal cancer patients in the era of multimodality management, with a focus on preoperative patient selection.

1

Research objectives per chapter

Part I. Neoadjuvant chemoradiotherapy

Chapter 2 To describe the short-term impact of neoadjuvant chemoradiotherapy on health-related quality of life before esophagectomy in esophageal cancer patients, and to study the impact of adverse events during neoadjuvant chemoradiotherapy on short-term health-related quality of life.

Chapter 3 To noninvasively quantify variation in intra-fraction motion of esophageal tumors over the course of neoadjuvant chemoradiotherapy using 2D cine-MRI series.

Chapter 4 To explore whether a higher neoadjuvant radiation dose could increase pathologic tumor response rates in esophageal cancer patients.

Part II. Treatment response assessment

Chapter 5 To evaluate the individual and combined value of repeated ^{18}F-FDG PET/CT and DW-MRI to predict pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer patients.

Chapter 6 To establish the optimal timing of DW-MRI scanning during neoadjuvant chemoradiotherapy for the prediction of pathologic complete response in patients with esophageal cancer.

Chapter 7 To develop a model that predicts the probability of pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer, based on DW-MRI, DCE-MRI and ^{18}F-FDG PET/CT.

Chapter 8 To assess the experienced burden associated with repeated MRI and PET/CT examinations during neoadjuvant treatment for esophageal cancer from the perspective of the patient.

Part III. Preoperative patient selection

Chapter 9 To describe the current and future perspectives in the surgical treatment of patients with esophageal cancer in the context of available literature.

Chapter 10 To describe the patients with esophageal cancer who do not proceed to surgical resection after starting neoadjuvant chemoradiotherapy.

Chapter 11 To determine whether the presence of generalized atherosclerotic calcification as determined on routine CT images is associated with anastomotic leakage after esophagectomy for cancer.

Chapter 12 To evaluate whether minimally invasive esophagectomy and gastrectomy can be safely applied in the acute setting.
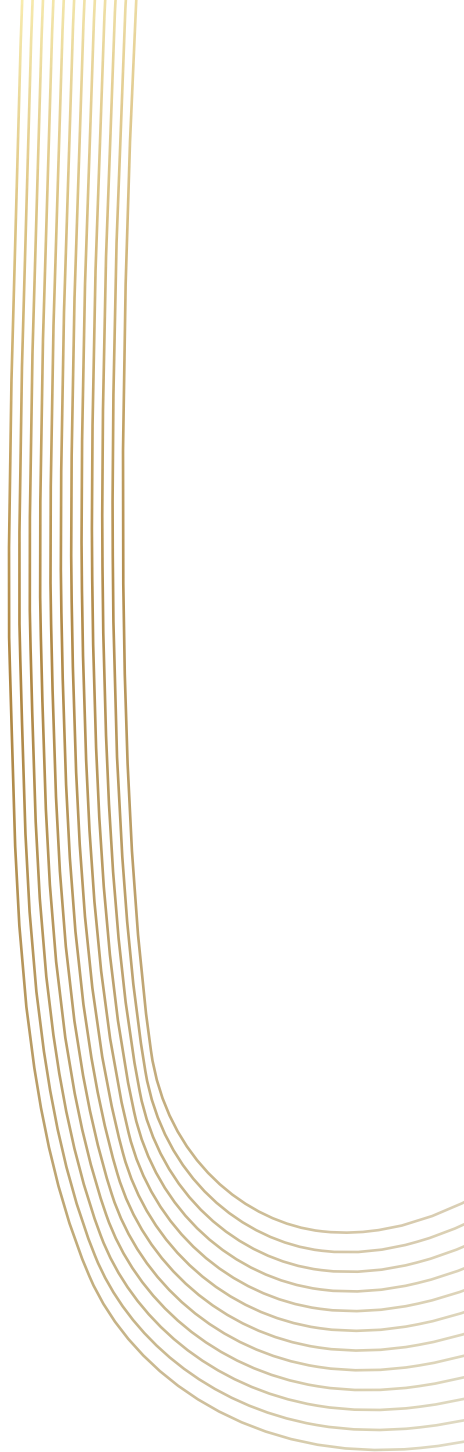
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1

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PART I

Neoadjuvant chemoradiotherapy

The impact of neoadjuvant chemoradiotherapy and related adverse events on short-term quality of life in esophageal cancer patients

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Abstract

Background
Insights into the impact of neoadjuvant chemoradiotherapy (nCRT) on short-term health-related quality of life (HRQOL) might be helpful for patients and physicians in the process of shared decision making. The aim of this study was to describe the short-term impact of nCRT on HRQOL before esophagectomy in esophageal cancer patients, and to study the impact of adverse events during nCRT on short-term HRQOL.

Methods
HRQOL was measured in patients with locally advanced esophageal cancer referred to the Department of Radiation Oncology before start of nCRT and 1 month after completion of nCRT, using EORTC questionnaires (QLQ-C30 and QLQ-OG25). Changes in HRQOL between baseline and follow up, were compared between patients with and without adverse events (CTCAE grade ≥ 3) during nCRT with mixed model analyses.

Results
In total 115 patients returned the baseline questionnaire of whom 85 patients (73.9%) returned the follow-up questionnaire. Adverse events during nCRT occurred in 30 patients (26.1%). During nCRT, physical functioning declined and fatigue increased, whereas odynophagia symptoms decreased at 1 month follow-up. General HRQOL remained stable. Adverse events during nCRT had a negative effect on dysphagia, pain and taste at follow-up.

Conclusion
Physical functioning and fatigue deteriorated in esophageal cancer patients treated with nCRT. The occurrence of adverse events during nCRT was associated with a sharper impairment of HRQOL and esophageal cancer specific symptoms.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is the preferred treatment for patients with locally advanced esophageal cancer, improving overall survival compared to esophagectomy alone.[1,2] In recent years, the emphasis on health-related quality of life (HRQOL) and other patient-reported outcome measures has enhanced, resulting in a more prominent role for both the quality and the quantity of life lived after cancer diagnosis.[3] This is reflected in the incorporation of HRQOL as an important endpoint when evaluating treatment efficacy, which is already executed in for example the ESOPEC trial comparing nCRT to perioperative chemotherapy for esophageal cancer.[4]

Regarding the long-term effects of nCRT, it is known that even though patients experience deterioration in HRQOL end-points after completion of nCRT, nCRT does not affect long-term HRQOL compared to surgery alone.[5–7] In contrast, severe complications after surgery have been consistently demonstrated to negatively impact HRQOL in the short and long term.[8–11] However, not only surgical treatment, but also treatment with nCRT is accompanied by serious (non-hematologic) adverse events in 13%.[2] The effect of nCRT on HRQOL has been described before[7,12], but insight is lacking in how adverse events during nCRT affect short-term HRQOL. This information could be used by physicians to adequately manage patients' expectations about their HRQOL shortly after nCRT, so that patients can anticipate on these effects and take proper measurement to cope with these problems.

Therefore, the aim of the current study was to describe the short-term impact of nCRT on HRQOL before esophagectomy in esophageal cancer patients, and to study how adverse events during nCRT impact short-term HRQOL.

Methods

This single center cohort study was reviewed and approved by the institutional review board of the University Medical Center Utrecht (number 11/515), and the need for written informed consent was waived.

Study population

Consecutive patients with histologically confirmed cancer of the esophagus or gastroesophageal junction who were scheduled to undergo nCRT followed by esophagectomy between October 2011 and August 2017 at the Department of Radiation Oncology were eligible for inclusion. Due to logistic reasons, only patients referred to the department from outside our center were sent questionnaires. Exclusion criteria included not completing the baseline questionnaire, completing the baseline questionnaire after starting nCRT and starting treatment other than nCRT.

Neoadjuvant treatment consisted of weekly intravenous administration of carboplatin area under the curve 2/paclitaxel 50 mg/m^2 for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy), as per the CROSS regimen.[2] Surgical resection was generally scheduled 6-8 weeks after neoadjuvant chemoradiotherapy according to the Dutch guidelines.[13]

Data regarding patient and tumor characteristics, as well as treatment-related variables were collected from a prospectively maintained database. Serious adverse events during nCRT were defined as adverse events grade 3 or higher according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE 4.0). Discontinuation of chemotherapy due to hematologic toxicity without the need for hospitalization or other interventions, as well as dysphagia for which tube feeding was started before nCRT were not included as serious adverse events.

Quality of life assessment

Eligible patients received self-report questionnaires by postal mail with their invitation for their first appointment (baseline), and 1 month after finishing nCRT (follow-up). Patients who did not return the baseline questionnaire were not invited to participate in the follow-up questionnaire. At both time points, 2 validated questionnaires were sent.

Cancer-specific HRQOL was measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30, version 3.0).[14] The structure of the QLQ-C30 has been reported in detail elsewhere and its validity and reliability has been examined in several diagnostic groups, including esophageal cancer patients.[15,16] Esophageal cancer specific HRQOL was measured by the EORTC QLQ-Oesophago-Gastric Module (QLQ-OG25).[17]

All scale and item scores from the QLQ-C30 and QLQ-OG25 were linearly transformed to a 0–100 score according to the EORTC scoring manuals.[18] High scores in the multi-item functional scales and the global quality of life scale indicated higher levels of function and quality of life (QLQ-C30), whereas higher scores on the symptom scales represented more symptoms (QLQ-C30, QLQ-OG25). For missing items from multi-item scales, the following was assumed as per recommendation of the developers: if at least half of the items from the scale had been answered, the missing items would have had values equal to the average of those items which were present for that patient.[18] The QLQ-C30 Summary Score[16] was only calculated for a respondent if all 13 scales contributing to that score were completed. In order to enhance the interpretation of the symptom scales of the QLQ-OG25, the percentage of symptomatic patients was calculated. Symptomatic refers to patients who answered 'a little', 'quite a bit', or 'very much' to any question within a scale or to a single item. Others were categorized as having no symptoms.[19]

Statistical analysis

Patient and treatment-related characteristics were presented as counts with percentages, means (± standard deviation [SD]) or medians (interquartile range [IQR]) where appropriate. Baseline HRQOL scale and symptom scores of all questionnaires were described as means with SD.

To compare HRQOL before and after administration of nCRT, linear mixed-effects models were used to calculate mean score differences (MDs) with 95% confidence intervals (CIs) between baseline and follow-up HRQOL scores, accounting for potential confounders. To assess the impact of occurrence of adverse events during nCRT on HRQOL scales, linear mixed-effects models were used with an adverse event-by-time interaction, accounting for potential confounders. All models included a patient-specific random intercept and were adjusted for the following confounding variables: age, sex, performance status, clinical T stage and clinical N stage. For the QLQ-C30 subscales, clinically relevant differences in HRQOL scores have been established before.[20] For the QLQ-OG25, no cut-off values had been established before. As such, MDs of 10-20 points were considered as moderate clinical difference and >20 points as large clinical difference.[21]

Lastly, in order to visualize differences in the distribution and probability density of the HRQOL scores at baseline and follow-up, as well as between patients with adverse events and without adverse events, rotated kernel density plots were constructed.

All statistical analyses were performed using R 3.5.1 open-source software ('PROscorer', 'lme4' and 'lmerTest' packages, www.R-project.org). In order to minimize the effect of multiple testing and type I errors, a two-sided p-value < 0.01 was deemed significant.

Results

Patients

Between October 2011 and July 2017, 115 patients who started neoadjuvant chemoradiotherapy for esophageal cancer completed the baseline questionnaire before starting nCRT (Figure 1). The mean age was 66.9 years (± SD: 7.3 years) and the majority (78.3%) was male (Table 1). Histologic tumor types mainly included adenocarcinoma (60.9%) and squamous cell carcinoma (35.7%). Severe adverse events during nCRT (CTCAE grade ≥ 3) occurred in 30 patients (26.1%) (Table 2).

The baseline questionnaire was completed 14 days (median, IQR: 10-17 days) before starting nCRT. Follow-up questionnaires after nCRT and before surgery were available in 85 patients (73.9%), and were completed 37 days (median, IQR: 35-43 days) after the last day of nCRT. The clinical characteristics of follow-up questionnaire responders and non-responders were similar, with the exception of the occurrence of severe adverse events (20.0% versus 43.3% respectively, Table 1).
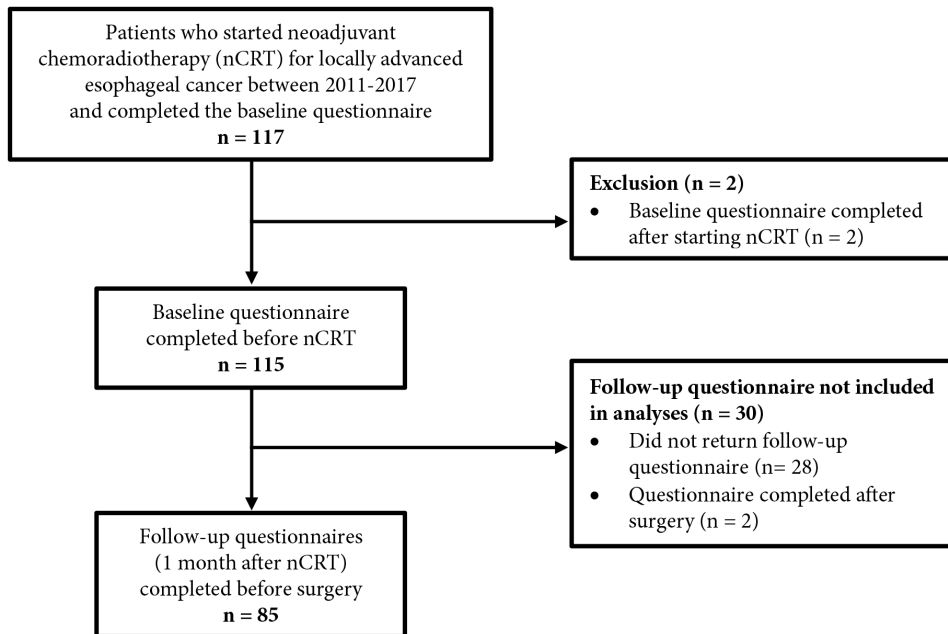
Figure 1. Flowchart

General quality of life

The HRQOL scales and items for QLQ-C30 are shown in Table 3. At baseline, global quality of life was highly skewed (Figure 2) with a mean score of 67 (SD ± 20). Fatigue (mean ± SD: 30 ± 24), insomnia (mean ± SD: 26 ± 28), pain (mean ± SD: 22 ± 22) and loss of appetite (mean ± SD: 21 ± 30) were the most prevalent general symptoms at baseline.

Global quality of life and general health scores were similar at baseline and 1 month after nCRT. Clinically relevant and statistically significant declines were however observed in physical functioning (MD [95% CI]: -8 [-12, -5]) and social functioning (MD [95% CI]: -8 [-13, -4]). Furthermore, patients experienced significantly more fatigue (MD [95% CI]: 7 [2, 11]) and dyspnea (MD [95% CI]: 10 [5, 14]) 1 month after nCRT. Absolute mean scores of HRQOL items and the available number of respondents per HRQOL item are provided in Supplementary Table 2.

Table 1. Clinical characteristics of the study population.

Characteristics	Full cohort (n = 115)		Baseline and follow-up questionnaire (n = 85)		Baseline questionnaire only (n = 30)	
	n	(%)	n	(%)	n	(%)
Age at diagnosis, in years (mean ± SD)	66.9 ± 7.3		67.3 ± 7.1		65.9 ± 9.7	
Sex						
Male	90	78.3%	71	83.5%	19	63.3%
Female	25	21.7%	14	16.5%	11	36.7%
WHO performance status						
0	53	46.1%	43	50.6%	10	33.3%
1	59	51.3%	41	48.2%	18	60.0%
2	3	2.6%	1	1.2%	2	6.7%
Clinical T stage[§]						
cT1[¶]	2	1.7%	1	1.2%	1	3.3%
cT2	17	14.8%	14	16.5%	3	10.0%
cT3	90	78.3%	67	78.8%	23	76.7%
cT4	6	5.2%	3	3.5%	3	10.0%
Clinical N stage[§]						
cN0	32	27.8%	24	28.2%	8	26.7%
cN1	60	52.2%	42	49.4%	18	60.0%
cN2	19	16.5%	15	17.6%	4	13.3%
cN3	4	3.5%	4	4.7%	0	0.0%
Tumor location						
Upper esophagus	4	3.5%	4	4.7%	0	0.0%
Middle esophagus	22	19.1%	14	16.5%	8	26.7%
Distal esophagus/gastroesophageal junction	89	77.4%	67	78.8%	22	73.3%
Histologic tumor type						
Adenocarcinoma	70	60.9%	56	65.9%	14	46.7%
Squamous cell carcinoma	41	35.7%	25	29.4%	16	52.3%
Other	4	3.5%	4	4.7%	0	0.0%
Adverse events of CTCAE grade ≥3 during neoadjuvant chemoradiotherapy	30	26.0%	17	20.0%	13	43.3%
Days between baseline questionnaire and start nCRT (median, IQR)	14 (10, 17)		14 (11, 17)		14 (5, 15)	
Days between end nCRT and follow-up questionnaire (median, IQR)	37 (35, 43)		37 (35, 43)		NA	

CTCAE Common Terminology Criteria of Adverse Events (version 4.0); *IQR* interquartile range; *NA* not applicable; *SD* standard deviation; *WHO* World Health Organization
[§] Clinical T and N stage are based on AJCC TNM 7th edition.
[¶] Both patients had a cT1N1 stage.

Table 2. Adverse events of CTCAE grade ≥3 during neoadjuvant chemoradiotherapy for esophageal cancer in the study population (baseline scores excluded).

Adverse events	Total (n=115)	
	n	%
All	30	26.1%
Dysphagia	13	11.3%
Leukopenia	4	3.5%
Thromboembolic event	3	2.6%
Nausea	3	2.6%
Vomiting	2	1.7%
Anorexia	2	1.7%
Febrile neutropenia	2	1.7%
Fatigue	1	0.9%
Esophageal perforation	1	0.9%
Dyspnea	1	0.9%
Allergic reaction	1	0.9%

Esophageal-specific symptoms

At baseline, the most pronounced esophageal cancer-specific symptom as measured by the QLQ-OG25 questionnaire was anxiety (99.1%, mean ± SD: 46 ± 19), followed by eating restrictions (87.0%, mean ± SD: 32 ± 23), odynophagia (85.8%, mean ± SD: 29 ± 23) and dysphagia (85.2%, mean ± SD: 24 ± 20) (Table 4, Figure 2). After nCRT, the most pronounced symptom remained anxiety (96.5%), followed by eating restrictions (65.1%) and trouble with coughing (63.9%). Clinically relevant and statistically significant effects of nCRT were observed in decreased odynophagia and decreased problems with eating in front of others (MD [95% CI]: -13 [-18, -9] and -10 [-15, -5], respectively).

Adverse events during nCRT and short-term quality of life

Patients who experienced a severe adverse event (CTCAE grade ≥ 3) had significantly more pain and discomfort, more advanced dysphagia scores and reported more trouble with taste after nCRT, compared to patients who did not experience adverse events (Table 4, Figure 3). Global quality of life after nCRT as measured by the QLQ-C30 and other symptom scales did not differ between patients with and without adverse events during nCRT (Table 3 and 4, Figure 3).

Table 3. Health-related quality of life (HRQOL)-scores of esophageal cancer patients before starting neoadjuvant chemoradiotherapy (nCRT) (baseline) and adjusted mean score differences 1 month after nCRT (follow-up), as well as at follow-up in patients who experienced adverse events during nCRT compared to patients without adverse events according to the EORTC QLQ-C30 questionnaire.

Quality of life dimension (QLQ-C30)	Baseline (n=115)		Follow-up (n=85)	Adverse events during nCRT
	Mean score	SD	Mean difference compared to baseline (95% CI)	Mean difference in follow-up HRQOL scores compared to patients without adverse events (95% CI)
Global quality of life[§]	67	20	2 (-2, 6)	-5 (-15, 5)
Functional scales[§]				
Physical functioning	85	17	**-8 (-12, -5)***	-7 (-16, 2)
Role functioning	77	27	-6 (-12, -1)	-10 (-25, 4)
Emotional functioning	70	20	5 (1, 9)	-10 (-21, 0)
Cognitive functioning	84	20	-1 (-5, 2)	-5 (-15, 4)
Social functioning	83	23	**-8 (-13, -4)***	-14 (-26, -2)
Symptom scales[¶]				
Fatigue	30	24	**7 (2, 11)***	13 (1, 24)
Nausea and vomiting	11	17	-1 (-6, 4)	4 (-5, 14)
Pain	22	22	-1 (-6, 5)	8 (-4, 21)
Single-item symptom scores[¶]				
Dyspnea	13	20	**10 (5, 14)***	1 (-11, 12)
Insomnia	26	28	-2 (-7, 3)	5 (-9, 19)
Loss of appetite	21	30	0 (-8, 7)	9 (-7, 24)
Constipation	15	26	-4 (-9, 2)	2 (-11, 14)
Diarrhea	5	15	4 (-1, 8)	-3 (-13, 6)
Financial difficulties	9	25	1 (-1, 4)	-3 (-14, 8)
QLQ-C30 Summary Score[§¥]	81	12	-2 (-5, 0)	-6 (-13, 1)

CI confidence interval, *nCRT* neoadjuvant chemoradiotherapy, *SD* standard deviation
Values in bold are both clinically relevant (Cocks et al.[20]) and statistically significant (*).
[§] Score range 0–100. Higher scores represent a better quality of life or higher level of functioning.
[¶] Score range 0–100. Higher scores represent more severe symptoms or problems.
* Statistically significant differences (p < 0.01) based on multivariable linear mixed effect models including a random intercept per patient and adjusted for age, sex, performance status, clinical T stage and clinical N stage.
[¥] Mean of all scores except for global quality of life and financial difficulties.[16]
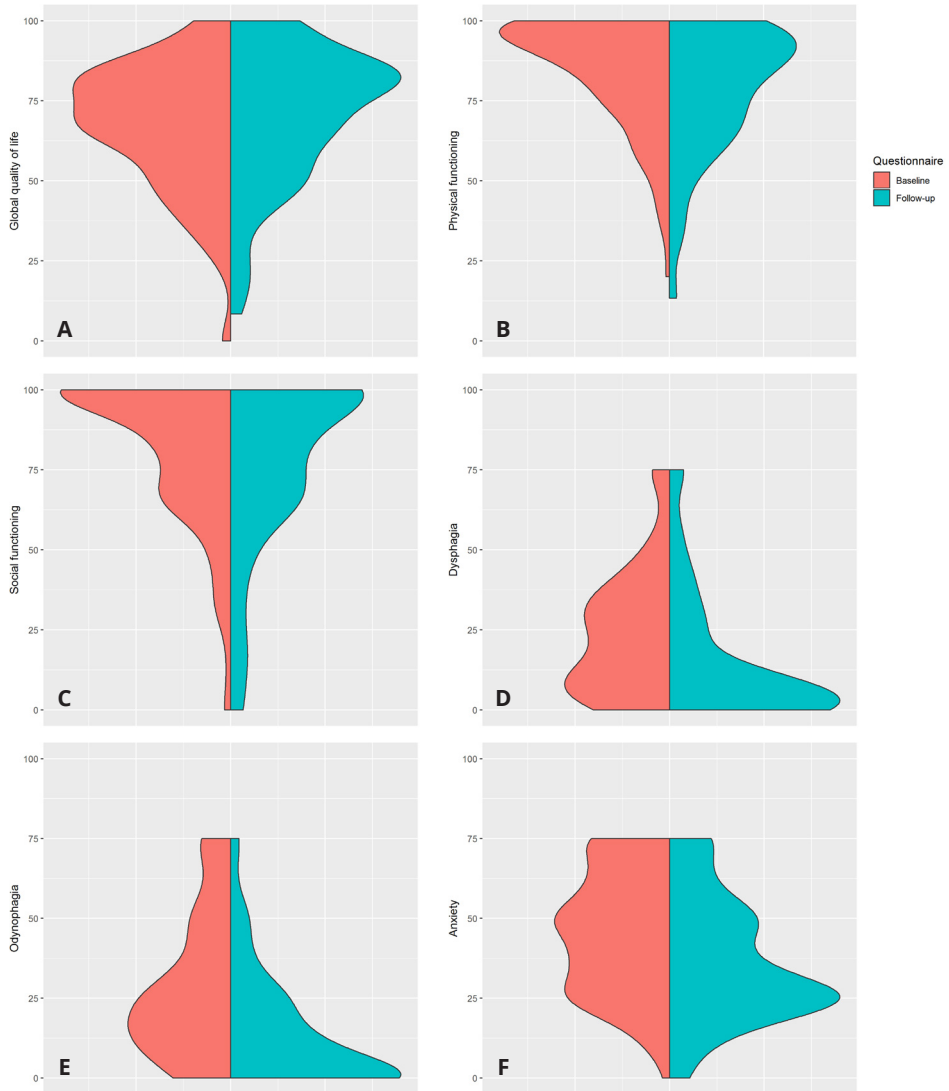
Figure 2. Rotated kernel density plots of global quality of life (*A*), physical functioning (*B*), social functioning (*C*) scales (according to the EORTC QLQ-C30 questionnaire) and dysphagia (*D*), odynophagia (*E*) and anxiety (*C*) symptoms (according to the EORTC QLQ-OG25 questionnaire) at baseline (before neoadjuvant chemoradiotherapy, *red*) and follow-up (1 month after neoadjuvant chemoradiotherapy, *blue*).

Table 4. Health-related quality of life (HRQOL)-scores of esophageal cancer patients before starting neoadjuvant chemoradiotherapy (nCRT) (baseline) and adjusted mean score differences 1 month after nCRT (follow-up), as well as at follow-up in patients who experienced adverse events during nCRT compared to patients without adverse events according to the EORTC QLQ-OG25 questionnaire.

Quality of life dimension (QLQ-OG25)	Baseline (n=115)			Follow-up (n=85)		Adverse events during nCRT
	Mean score	SD	Symptomatic (%)§	Mean difference compared to baseline (95% CI)	Symptomatic (%)§	Mean difference in follow-up HRQOL scores compared to patients without adverse events (95% CI)
Multi-item symptom scales¶						
Dysphagia	24	20	85.2%	-7 (-11, -3)*	57.1%	**14 (3, 24)***
Eating restrictions	32	23	87.0%	-7 (-12, -2)*	65.1%	9 (-3, 20)
Reflux	5	13	18.3%	-1 (-4, 2)	13.3%	3 (-4, 9)
Odynophagia	29	23	85.8%	**-13 (-18, -9)***	47.5%	5 (-6, 16)
Pain and discomfort	14	18	44.7%	-4 (-8, 0)	25.0%	**14 (5, 23)***
Anxiety	46	19	99.1%	-8 (-11, 4)*	96.5%	5 (-4, 15)
Single-item symptom scores¶						
Eating in front of others	21	26	46.4%	**-10 (-15, -5)***	23.5%	1 (-12, 13)
Dry mouth	13	21	33.9%	4 (-1, 9)	42.4%	7 (-4, 19)
Trouble with taste	8	17	22.8%	9 (4, 14)*	40.0%	**15 (5, 25)***
Body image	8	16	21.1%	5 (1, 8)	29.4%	5 (-4, 14)
Trouble swallowing saliva	12	23	27.0%	-2 (-7, 2)	24.7%	-1 (-12, 10)
Choking when swallowing	6	14	20.0%	0 (-4, 3)	18.8%	0 (-8, 7)
Trouble with coughing	20	20	61.4%	4 (-1, 9)	63.9%	14 (3, 24)
Trouble talking	4	11	13.9%	2 (-1, 5)	13.3%	4 (-3, 10)
Weight loss	23	27	52.9%	-3 (-8, 2)	51.2%	8 (-5, 20)

CI confidence interval, SD standard deviation

Values in bold are both clinically relevant (mean difference ≥10 points) and statistically significant (*).

§ Symptomatic refers to patients who answered 'a little', 'quite a bit', or 'very much' to any question within a scale or to a single item. Others were categorized as having no symptoms.[19]

¶ Score range 0–100. Higher scores represent more severe symptoms or problems.

* Statistically significant differences (p < 0.01) based on multivariable linear mixed effect models including a random intercept per patient and adjusted for age, sex, performance status, clinical T stage and clinical N stage.
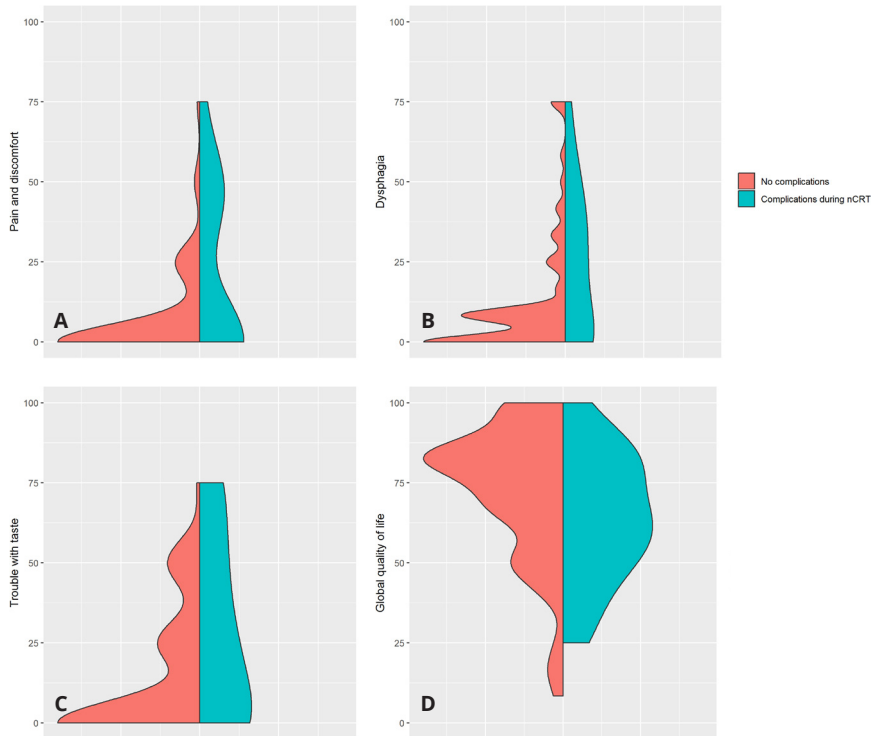
Figure 3. Rotated kernel density plots of pain and discomfort (QLQ-OG25, *A*), dysphagia (QLQ-OG25, *B*), trouble with taste (QLQ-OG25, *C*) and global quality of life (QLQ-C30, *D*) at follow-up (1 month after neoadjuvant chemoradiotherapy) for patients without adverse events during nCRT (*red*) and with adverse events during nCRT (*blue*).

Discussion

This study was designed to assess the short-term effect of nCRT and more specifically, adverse events during nCRT, on global and esophageal cancer-specific HRQOL in patients with locally advanced esophageal cancer. In general, the impact of nCRT on global HRQOL 1 month after nCRT was demonstrated to be small. There was a decline in physical and social functioning, and more fatigue and dyspnea. The impact of nCRT on esophageal cancer-specific symptoms was moderately positive on some symptom scales (i.e., less odynophagia and less problems with eating in front of others). Moreover, patients who experienced adverse events during nCRT reported significantly more dysphagia, pain, trouble with taste and declined social functioning. These results extend our knowledge on the impact of nCRT on HRQOL, and are of important clinical value in informed decision-making. The results of our study could be helpful for clinicians to

meet patients' expectations and facilitate informed decision-making best if HRQOL, cure rates and morbidity are emphasized.[22]

Also, the analysis of HRQOL during the entire treatment pathway of esophageal cancer may identify hidden critical points that may help to plan the best management of these patients. Interestingly, global quality of life was not affected by adverse events during nCRT, but esophageal cancer specific symptoms and social functioning were. These findings suggest that increased attention for fast and adequate treatment of adverse events and symptom management, such as pain management, in the period after nCRT in these patients may be useful to improve HRQOL.

Notably, nearly all patients indicated that they experienced any form of anxiety before and after nCRT. Even though the percentages might be slightly misleading since they indicate the number of patients responding at least with 'a little' in at least one of the items, these findings indicate that it might be beneficial to provide additional psychological support after the first consultation with the treatment team. Emotional well-being did not deteriorate significantly after nCRT or in patients with adverse events, but was lower than in the general Dutch population (mean score at baseline ± SD: 70 ± 20 versus 89 ± 16 in the reference population).[23,24] It is important to realize that baseline HRQOL assessment in the current study was obtained shortly after diagnosis with esophageal cancer. As such, the true effect of the disease and its' treatment on HRQOL can only be adequately assessed when surrogates of true baseline HRQOL scores (in patients without esophageal cancer diagnosis) are obtained from population-based references values.[19,23,24] This is reflected by the fact that global quality of life was already lower at baseline in the current study population than in the healthy Dutch reference population (mean score at baseline ± SD: 67 ± 20 versus 78 ± 17 in the reference population).[23,24]

It has been demonstrated before that esophageal cancer patients experience a short-term deterioration in HRQOL immediately (± 1 week) after completion of nCRT.[7,12] This decline is explained by expected persisting adverse effects and therefore maximum toxicity of chemotherapy and radiotherapy, such as fatigue, esophagitis, and hematologic toxicity. The current study does no longer demonstrate a decline in global HRQOL 1 month after nCRT, but decreased physical functioning and more fatigue persist, even though the effects are smaller than reported immediately after completion of nCRT.[7] As such, patients might not have reached their full recovery phase from nCRT yet. Decreased physical functioning and increased fatigue are likely also the cause of more dyspnea 1 month after nCRT, as this is expected to be too soon to be a symptom of radiation-induced lung injury.[25] This finding should also be considered when determining the optimal timing for subsequent surgical resection, with the aim to schedule esophagectomy at least 1 month after nCRT according to a patient's self-evaluation of their physical condition.

Some limitations of the current study deserve attention. HRQOL research by means of

self-report questionnaires is inherently hampered by selection bias due to non-participation or missing data. Unfortunately, due to logistic reasons, the response rate of the baseline questionnaire in the current study could not be accurately determined. This might have attributed to selection bias as well, although there are no signs that the current study population differs substantially in terms of clinical characteristics from 2 Dutch reference cohorts of patients who underwent neoadjuvant chemoradiotherapy (Supplementary Table 1), nor from the commonly reported Western esophageal cancer population. Furthermore, there is no obvious reason to assume that patients referred directly to our department from outside our center would differ greatly from the patients who are referred from other departments within our center in terms of HRQOL. Also, the response rate of the follow-up questionnaire was quite high (75.6%), but associated with the occurrence of adverse events during nCRT. This could imply that the reported declines in the several studied aspects of HRQOL might have been slightly underestimated.

Strengths of the current study include the relatively large and homogenous sample size, as well as the inclusion of both the QLQ-C30 and the QLQ-OG25 questionnaire. It is known that scales in the QLQ-C30 and the QLQ-OG25 are not associated, as these assess different aspects of HRQOL.[17] Therefore, the use of a modular approach for the assessment of HRQOL in this study is essential to detect both benefits and disadvantages of nCRT.

Another important strength of the study is that the analyses studying the impact of nCRT on HRQOL as well as the analyses studying the impact of adverse events during nCRT on HRQOL account for known confounding variables, resulting in the direct effect of nCRT and adverse events on HRQOL.

In summary, this study is a step towards enhancing the understanding of the short-term impact of nCRT and related adverse events on HRQOL in esophageal cancer patients. The results from this study indicate that the impact of nCRT on general quality of life 1 month after nCRT is small, but effects on physical functioning, as well as fatigue are present 1 month after nCRT. Furthermore, as expected, patients with adverse events during nCRT reported more dysphagia and pain symptoms. These results support informed decision-making, especially for patients who fear the negative effect of neoadjuvant treatment. In addition, these results support the incorporation of HRQOL as important endpoints when evaluating treatment efficacy.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Clinical characteristics of the study population (patients who started neoadjuvant chemoradiotherapy for esophageal cancer and returned the baseline questionnaire) compared to the clinical characteristics of 2 Dutch reference cohorts.

Characteristics	Study cohort (n = 115)		UMCU reference cohort 2011-2017 (n = 211)[⁋]		Dutch reference cohort 2015-2016 (n = 1521)[¥]	
	n	(%)	n	(%)	n	(%)
Age at diagnosis, in years (mean ± SD)	66.9 ± 7.3		64.5 ± 8.0		65.1 ± 8.8	
Sex						
Male	90	78.3%	159	75.4%	1191	78.3%
Female	25	21.7%	52	24.6%	330	21.7%
WHO performance status						
0	53	46.1%			798	52.5%
1	59	51.3%	NA		462	30.4%
2	3	2.6%			38	2.5%
Clinical T stage[§]						
cT1	2	1.7%	3	1.4%	22	1.4%
cT2	17	14.8%	36	17.1%	458	30.1%
cT3	90	78.3%	169	80.1%	981	64.5%
cT4	6	5.2%	3	1.4%	22	1.4%
Unknown	NA		NA		38	2.5%
Clinical N stage[§]						
cN0	32	27.8%	60	28.4%	602	39.6%
cN1	60	52.2%	103	48.8%	575	37.8%
cN2	19	16.5%	38	18.0%	282	18.5%
cN3	4	3.5%	10	4.7%	40	2.6%
Unknown	NA		NA		22	1.4%
Tumor location						
Upper esophagus	4	3.5%	7	3.3%	14	0.9%
Middle esophagus	22	19.1%	32	15.2%	176	11.6%
Distal esophagus/gastroesophageal junction	89	77.4%	172	81.5%	1279	84.1%
Esophagus not otherwise specified	NA		NA		52	3.4%
Histologic tumor type						
Adenocarcinoma	70	60.9%	143	67.8%	1202	79.0%
Squamous cell carcinoma	41	35.7%	67	31.8%	319	21.0%
Other	4	3.5%	1	0.5%	NA	

NA not applicable/available; *SD* standard deviation; *WHO* World Health Organization

[§] Clinical T and N stage are based on AJCC TNM 7th edition.

[⁋] Reference cohort of patients who underwent neoadjuvant chemoradiotherapy followed by esophagectomy for esophageal cancer at the University Medical Center Utrecht during 2011-2017.

[¥] Reference cohort of patients who started neoadjuvant chemoradiotherapy for esophageal cancer in the Netherlands in 2015-2016, based on the Netherlands Cancer Registry (as reported on by Borggreve et al. *Frequency of surgical resection after starting neoadjuvant chemoradiotherapy in patients with esophageal cancer: A population-based cohort study.* European Journal of Surgical Oncology 2019).

Supplementary Table 2. Mean scores and available number of patient-reported outcomes per health-related quality of life (HRQOL)-scale before starting neoadjuvant chemoradiotherapy (baseline) and 1 month after neoadjuvant chemoradiotherapy (follow-up).

Quality of life dimension	Baseline (n=115)			Follow-up (n=85)		
	n	Absolute mean score	SD	n	Absolute mean score	SD
QLQ-C30						
Global quality of life[§]	115	67	20	85	71	21
Functional scales[§]						
Physical functioning	115	85	17	85	78	20
Role functioning	115	77	27	85	73	29
Emotional functioning	114	70	20	85	76	23
Cognitive functioning	114	84	20	85	85	18
Social functioning	114	83	23	85	77	28
Symptom scales[¶]						
Fatigue	114	30	24	85	34	24
Nausea and vomiting	114	11	17	85	9	21
Pain	115	22	22	85	19	27
Single-item symptom scores[¶]						
Dyspnea	115	13	20	84	21	25
Insomnia	114	26	28	85	23	30
Loss of appetite	114	21	30	83	18	29
Constipation	113	15	26	84	11	21
Diarrhea	114	5	15	85	9	21
Financial difficulties	112	9	25	84	9	24
QLQ-C30 Summary Score[§¥]	113	81	12	82	81	16
QLQ-OG25						
Multi-item symptom scales[¶]						
Dysphagia	115	24	20	84	14	20
Eating restrictions	115	32	23	83	22	23
Reflux	115	5	13	83	4	11
Odynophagia	113	29	23	80	13	18
Pain and discomfort	114	14	18	84	9	18
Anxiety	115	46	19	85	37	19
Single-item symptom scores[¶]						
Eating in front of others	112	21	26	81	8	18
Dry mouth	115	13	21	85	16	22
Trouble with taste	114	8	17	85	16	23
Body image	114	8	16	85	11	21
Trouble swallowing saliva	115	12	23	85	10	20
Choked when swallowing	115	6	14	85	6	14
Trouble with coughing	114	20	20	83	22	22
Trouble talking	115	4	11	83	5	14
Weight loss	115	23	27	84	18	22

SD standard deviation
[§] Score range 0–100. Higher scores represent a better quality of life or higher level of functioning.
[¶] Score range 0–100. Higher scores represent more severe symptoms or problems.
[¥] Mean of all scores except for global quality of life and financial difficulties.

Quantification of variations in intra-fraction motion of esophageal tumors over the course of neoadjuvant chemoradiotherapy based on cine-MRI

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Abstract

Purpose
To noninvasively quantify variations in intra-fraction motion of esophageal tumors over the course of neoadjuvant chemoradiotherapy (nCRT) using 2D cine-magnetic resonance imaging (MRI) series.

Material and Methods
Patients treated with nCRT for esophageal cancer underwent 6 MRI scans. Scans were acquired prior to the start of nCRT, followed by weekly MRI scans during nCRT. Cine-MRI series were acquired in the coronal and sagittal plane ($\approx$1.6Hz). To be able to quantify intra-fraction motion over a longer time period, a second cine-MRI series was performed after 10 minutes. Tumor motion was assessed in cranio-caudal (CC), anterior-posterior (AP) and left-right (LR) direction. Motion patterns were analyzed for the presence of deep inhales and tumor drift.

Results
A total of 232 cine-MRI series of 20 patients were analyzed. The largest tumor motion was found in CC direction, with a mean peak-to-peak motion of 12.7 mm (standard deviation [SD] 5.6), followed by a mean peak-to peak motion in AP direction of 3.8 mm (SD 2.0) and in LR direction of 2.7 mm (SD 1.3). The CC intra-fraction tumor motion can differ extensively between and within patients. Deep inhales were present in 6 of 232 scans (3%). After exclusion of these scans, mean CC peak-to-peak motion was 12.3 mm (SD 5.2). Correction for tumor drift showed a further reduction to 11.0 mm (SD 4.6). Despite correction for tumor drift, large variation in tumor motion occurred within patients during treatment. Mean tumor drift during the 10 minute interval between the 2 series was 1.5 mm (SD 1.8), with a maximum of 11.6 mm.

Conclusions
Intra-fraction tumor motion was found to be highly variable between and within patients with esophageal cancer over the course of nCRT. Correction for deep inhales and tumor drift reduced peak-to-peak motion. The stochastic nature of both deep inhales and tumor drift indicates that real-time tumor motion management during radiotherapy is a prerequisite to safely reduce treatment margins.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection is widely accepted as standard treatment with curative intent for patients with resectable esophageal cancer.[1-3] Due to the presence of positioning uncertainties and respiratory motion, substantial CTV-to-PTV margins (typically ranging from 10 mm to 15 mm) are currently applied.[1] Smaller CTV-to-PTV margins would result in a reduced radiation dose to the surrounding healthy tissues, and would thereby reduce short- and long-term complications. Furthermore, smaller margins could be used to increase the dose to the tumor, while maintaining the dose constraints for healthy tissues that are currently used. In order to develop highly conformal treatment plans with adequate tumor coverage, the irradiation field needs to be adapted to tumor movement. As such, information about (variations in) tumor movement over the course of nCRT is desired.

To date, several imaging modalities have been used to assess tumor motion in esophageal cancer patients. Drawbacks of these studies using four dimensional computed tomography (4DCT) to quantify esophageal tumor motion[4-7] are the additional exposure to radiation and the need for invasive placement of fiducial markers. Furthermore, 4DCT studies only provide information on the average tumor motion as observed during CT acquisition, but not on variations in the tumor motion during scanning. This is due to the reconstruction of 4DCT scans in which the tumor motion is binned in a defined number of respiratory phases or amplitudes after acquisition, resulting in the reconstruction of only one breathing cycle in 4DCT. Therefore it is not possible to measure tumor drift with 4DCT, as measurement of this process requires reconstruction of multiple breathing cycles.

Esophageal tumor motion can also be visualized with magnetic resonance imaging (MRI). In cine-MRI, subsequent 2D images are acquired with a high temporal resolution, which is widely used to study motion patterns in different tumor sites.[8-10] A mean cranio-caudal peak-to-peak motion of 13.3 mm with a wide range of 2.7 to 24.5 mm was found using cine-MRI, in which the mobility of distal tumors was generally larger than that of more proximal tumors.[11]

In previous studies either four-dimensional cone-beam CT (4D-CBCT) was used over the course of treatment to quantify variations in tumor motion, or MRI was used at a single time point prior to treatment. As mentioned above, the disadvantage of 4DCT imaging is that it does not give information about possible tumor drift. Therefore, the purpose of our observational study was to quantify variations in intra-fraction esophageal tumor motion over the course of nCRT within the same patient, using weekly cine-MRI series. Insight in motion patterns of esophageal tumors could be used to determine which motion management strategy (e.g. tumor tracking, tumor gating, dynamic planning)[12,13] may be the most appropriate for on-line MRI-guided radiotherapy.[14,15] Furthermore, if tumor

motion prior to treatment is a reliable indicator for tumor motion during treatment, personalized PTV margins could be used in future clinical practice.

Methods and Materials

Study population

Patients with histologically confirmed esophageal cancer who were planned to receive nCRT followed by surgery were eligible for inclusion. Neoadjuvant chemoradiotherapy consisted of 5 weeks of treatment, involving weekly intravenous administration of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy) according to the CROSS regimen.[1] Standard diagnostic work-up consisted of endoscopy with biopsies of the primary tumor site, as well as integrated ^{18}F-FDG-PET/CT for clinical staging. Patients with contraindications for MRI were not eligible for inclusion. The study was approved by the local medical ethics committee and written informed consent was obtained from all patients.

MRI acquisition

MRI images were acquired at 6 time points; prior to the start of nCRT, followed by weekly MR scans during the course of nCRT. All images were acquired on a 1.5T Philips Ingenia (Best, the Netherlands), using the Anterior/Posterior (28 channel) receive coils. Patients were positioned in supine position with both arms next to the body. Respiratory-triggered sagittal and transverse anatomical T_2-weighted scans were acquired with a multi-slice turbo spin echo sequence (tT_2W: TR/TE = 1983/100ms, sT_2W: TR/TE = 1432/100ms, resolution = 0.67x0.67x4mm^3). These scans served as reference to plan 2 cine-MRI series: one coronal and one sagittal cine-MRI series To prevent substantial out-of-plane motion the scanning plane of the coronal cine-MRI series was angulated, such that it was aligned with the largest extent of the tumor in the sagittal T_2-weighted scan. For the sagittal cine-MRI series, the scanning plane was positioned through the center of the tumor, which was identified using the transverse T_2-weighted scan. The images were both acquired with a resolution of 2.01x2.01mm and 5 mm slice thickness, during 46 seconds of free breathing (1.6Hz) for the coronal and 43 seconds (1.7Hz) for the sagittal series. In order to quantify the difference in intra-fraction tumor motion and drift within one scanning session, both coronal and sagittal cine-MRI series were acquired twice during each scanning session: the first series was initiated after approximately 20 minutes of scanning and the second series after scanning a diffusion-weighted (DW-) MR series (10 minutes). These DW-MR scans included a b-value of 800 s/mm^2 (SPIR fat suppression, resolution = 3.25x3.25x4mm^3, bandwidth per pixel = 22.9Hz).[16]

Motion characterization

The primary tumor was delineated on the initial b800 s/mm^2 DW-MRI, using an automated contouring algorithm based on clustering (ITK-SNAP[17]). Afterwards, this delineation was verified using the transverse T$_2$W scan (tT$_2$W). For each of the subsequent time points (2 to 6) a rigid registration between the tT$_2$W scan and the tT$_2$W baseline scan was performed in Elastix (Version 4.7).[18] Using this registration, the tumor delineation of the first time point was propagated to the other time points (2 to 6) and manually adjusted if necessary (e.g. in case of shrinkage of the esophageal circumference). Next, all tumor delineations were propagated to the corresponding 2D cine-MRI series. An optical flow algorithm (RealTITracker[19,20]) was used to quantify tumor motion on the cine-MRI series. Corresponding motion vector fields were calculated for each frame with respect to a reference frame and evaluated within the delineated tumor volume. The reference frame was manually selected from 6 consecutive frames in such a way that the shape of the tumor resembled the tumor delineation as performed on the initial b800 scan as closely as possible. Motion was evaluated in cranio-caudal (CC), left-right (LR) and anterior-posterior (AP) directions (Matlab, The Mathworks Inc, Natick, Massachusetts, USA). The angulation of the coronal scanning plane was taken into account for the calculation of the CC-motion, such that the true CC-motion was calculated. Peak-to-peak amplitudes of tumor motion were calculated in all three directions. Furthermore, the smallest range to include 95% of the data points (excluding 5% most extreme data points) was calculated (C95). This C95 is a more robust measure for tumor motion as it excludes outliers caused by sporadic movement (e.g. sneezing, hiccups) as seen on the cine-MRI series. CC-motion patterns analyses were divided into short- and long-term intra-fraction motion (see Figure 1 for schematic overview of timeline and terminology).

Short-term intra-fraction motion was defined as the motion occurring within one cine-MRI series of 45 seconds, in which the presence of deep inhales and tumor drifting or irregular motion patterns were quantified. To estimate the effect of deep inhales on the motion curves, the minimum value (0th percentile, P0) and 10th percentile (P10) were compared. No large P10-P0 differences were expected in a regular breathing curve. However, in a curve in which a deep inhale occurs (presenting as a negative peak in a motion curve), a large difference in P10-P0 was expected.

To determine the presence of tumor drift in motion curves, drift lines were estimated. These drift lines were defined as the mid-position (mean) between consecutively found local maxima and minima in the motion curve. This drift line was subtracted from the motion curve, after which the difference in peak-to-peak and C95 amplitude for both curves functioned as a measure for the presence of a drift.

Long-term intra-fraction motion was defined as the motion which occurred within the 10 minute time-interval between the 2 cine-MRI series. This was quantified as the shift between

the initial drift lines (first 6 data-points) of both the first and second cine-MRI series. This can be interpreted as a conservative surrogate for the displacement of the esophageal tumor between set-up of the patient and final dose delivery. In which a positive long-term drift represents a movement in cranial direction.

Statistical analysis

This study was of descriptive nature and therefore no formal sample size calculation was performed. All visual representations were generated using GraphPad Prism 6.07 software (GraphPad Software, La Jolla, California, USA) and statistical analysis was performed in SPSS Statistics version 22 (IBM Corp., Armonk, New York, USA). The mean and standard deviation (SD) of the peak-to-peak and C95 amplitude for the whole group were calculated.
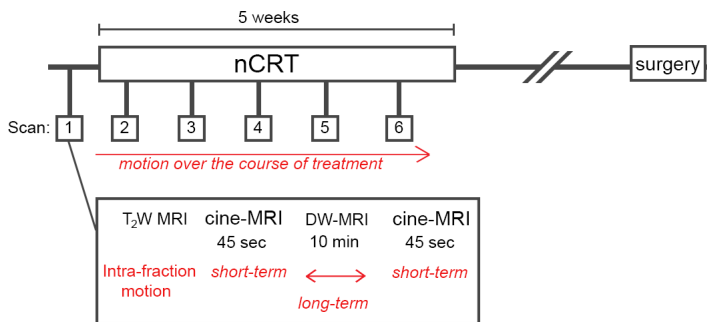
Figure 1. Overview of treatment and scanning timeline including a schematic representation of terminology used for indication of intra-fraction motions quantified in this study.

Results

Study population

A total of 25 consecutive patients were included, with MR scans acquired between April 2016 and October 2017. Five patients were excluded for analysis due to small tumor volume (<7ml, n=1), poor tumor visibility on MRI (n=3) or withdrawal of informed consent (n=1), resulting in a total of 20 patients suitable for analysis. In 3 of the included 20 patients, one of the weekly MR-scans during nCRT was incomplete or missing due to the condition of the patient. In 2 patients the second cine-MR series was not available at one time point. This led to a total amount of 232 acquired cine-MRI series for the total study population. All patients were male (20/20) with a mean age of 66.6 years (SD 6.9). Two patients had a mid-esophageal tumor (patient 1 and 2), 15 patients a distal esophageal tumor (patients

3-17), whereas the remaining 3 patients had a gastroesophageal junction tumor (patients 18-20). Patient and tumor characteristics are summarized in Table 1.

Tumor motion

A coronal cine-MRI frame together with the estimated CC and LR motion is shown in Figure 2. This figure shows excellent visualization of the thorax and abdomen at 1.5T, enabling motion characterization. The largest intra-fraction esophageal tumor motion was found in CC direction with a mean peak-to-peak motion of 12.7 mm (SD 5.6, range 4.4-33.7). The mean AP peak-to-peak motion was 3.8 mm (SD 2.0, range 0.7-10.2). The least motion was seen in LR direction, with a mean peak-to-peak of 2.7 mm (SD 1.3, range 0.7-8.3). The calculated peak-to-peak and C95 in the CC-direction for the whole group is summarized in Table 2. Since CC-motion was 22% less on average when calculated on sagittal images, analyses were only performed on the coronal cine-MRI series.

Table 1. Patient characteristics

	Full cohort (n=20)	
Characteristic	n	%
Gender		
Male	20	(100%)
Age (at start treatment), years (mean ± SD)	66.6 ± 6.9	
Clinical T-status		
T2	1	(5%)
T3	19	(95%)
Clinical N-status		
N0	7	(35%)
N1	9	(45%)
N2	3	(15%)
N3	1	(5%)
Histopathology		
Squamous cell carcinoma	4	(20%)
Adenocarcinoma	15	(75%)
Undifferentiated carcinoma	1	(5%)
Location		
Proximal third of esophagus	0	(0%)
Middle third of esophagus	2	(10%)
Distal third of esophagus	15	(75%)
Gastroesophageal junction	3	(15%)
Volume planning GTV (ml)		
Mean (± SD)	50.9 ± 25.5	
Range	19.0 - 126.3	

GTV gross tumor volume, *SD* standard deviation
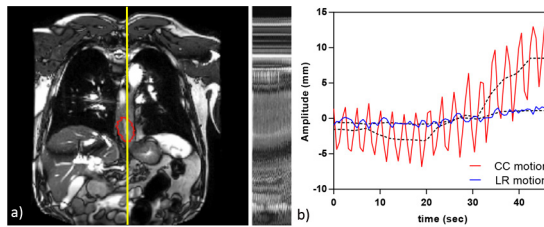
Figure 2. (A) A cine-MRI scan of a patient with the tumor delineation in red. On the right side the 75 time frames are visible corresponding to the location of the yellow line in the image. **(B)** Amplitude of the tumor motion in cranio-caudal (CC, *red*) and left-right direction (LR, *blue*). The black dashed lines show the estimated drift lines.

Table 2. Cranio-caudal tumor motion

Motion	All data (n=232)			Deep inhale exclusion (n=226)			Drift corrected (n=226)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Peak-to-peak (mm)	12.7	5.6	4.4-33.7	12.3	5.2	4.4-28.1	11.0	4.6	4.1-26.6
C95 (mm)	10.9	4.8	3.5-27.3	10.6	4.6	3.5-26.7	9.8	4.0	3.9-25.4

C95 the smallest range to include 95% of the data points (excluding 5% most extreme data points), *SD* standard deviation

Typical CC tumor motion curves are presented in Figure 3. Curves with long-term intra-fraction drift (patient 1) and short-term intra-fraction drift (patient 4), as well as regular (patient 2) and irregular motion behavior (patient 15) are depicted. The variety of tumor motion for the entire patient group is visualized in Figure 4a, in which the peak-to-peak amplitude is shown in each patient for the 2 scans for each time point separately. As illustrated by Figure 4a, the average intra-fraction tumor motion can differ extensively between patients, and large variations of intra-fraction motion are seen within some patients. Furthermore, it indicates that amplitude prediction for tumor motion throughout the treatment course based on the initial two baseline series (blue line represent mean initial amplitude), creates a risk of severe overestimation (patient 7) or underestimation (patient 4).

Short-term intra-fraction motion

Analysis of the CC motion patterns based on the P10 and P0 revealed presence of deep inhales in 6 of the 232 series (3%). In these 6 cine-MRI series, the magnitude of the tumor motion during these inhales was 2 times larger than that of the remaining tumor motion, and the P10-P0 value was more than 3 times the standard deviation above the mean of all 232 series. Results of the short-term drift correction, using the drift lines within the series,
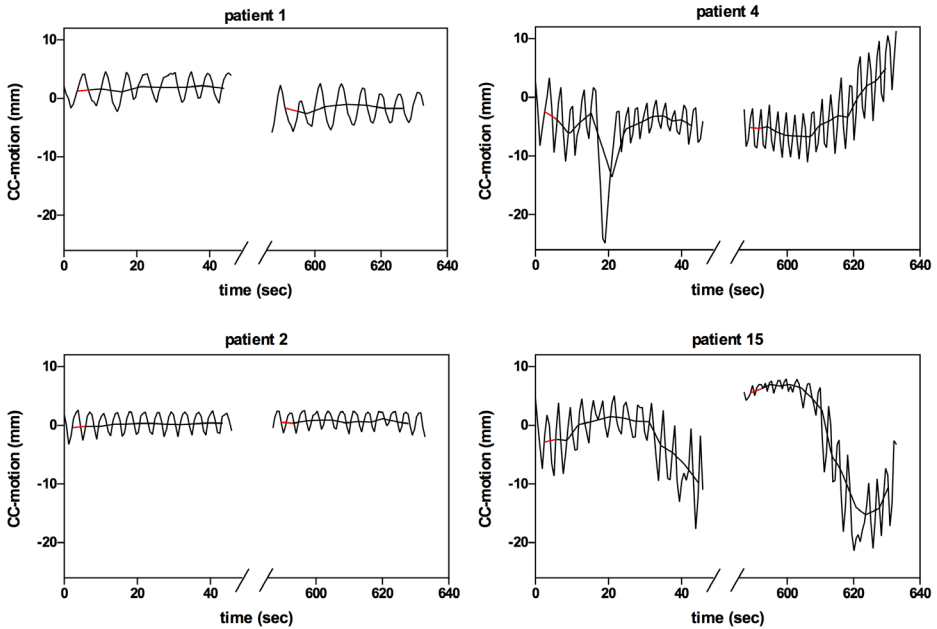
Figure 3. Four examples of motion curves with different behavior are visualized. Patient 1: a long-term drift between series. Patient 2: very regular motion. Patient 4: a deep inhale and short-term drift. Patient 15: irregular motion behavior in both series. The first 6 data-points in each drift line, indicated in red, were used to quantify the long-term drift.

are visualized in Figure 4b. A mean reduction in peak-to-peak amplitude of 1.3 mm (SD 1.8) was found. The largest short-term drift was present in patient 15 (-12.4 mm), which was verified by visual inspection of the cine-MRI series and is also depicted in Figure 3 (second series). Since a drift line correction does not compensate for deep inhales, the 3 large amplitudes in the CC motion of patient 7 - caused by 3 deep inhales - remained. As the presence of these deep inhales obscured the effect of the drift line correction, cine-MRI series including deep inhales were excluded. Peak-to-peak and C95 motion amplitudes, as well as the corresponding drift-corrected amplitudes after exclusion of series with deep inhales are presented in Table 2. A mean peak-to-peak motion of 11.0 mm (SD 4.6, range 4.1-26.6) was found after exclusion of deep inhales and drift correction. The decrease in peak-to-peak motion after deep inhale exclusion and drift correction is also visualized in Figure 5. After drift correction, 49% of the scans showed a maximum peak-to-peak amplitude smaller than 10 mm, compared to 38% before drift correction. Before any correction the peak-to-peak amplitude of 95% of the fractions fell within 24.6 mm, this measure of intra-fraction motion was reduced with 5.2 mm if deep inhale exclusion and drift correction was applied.
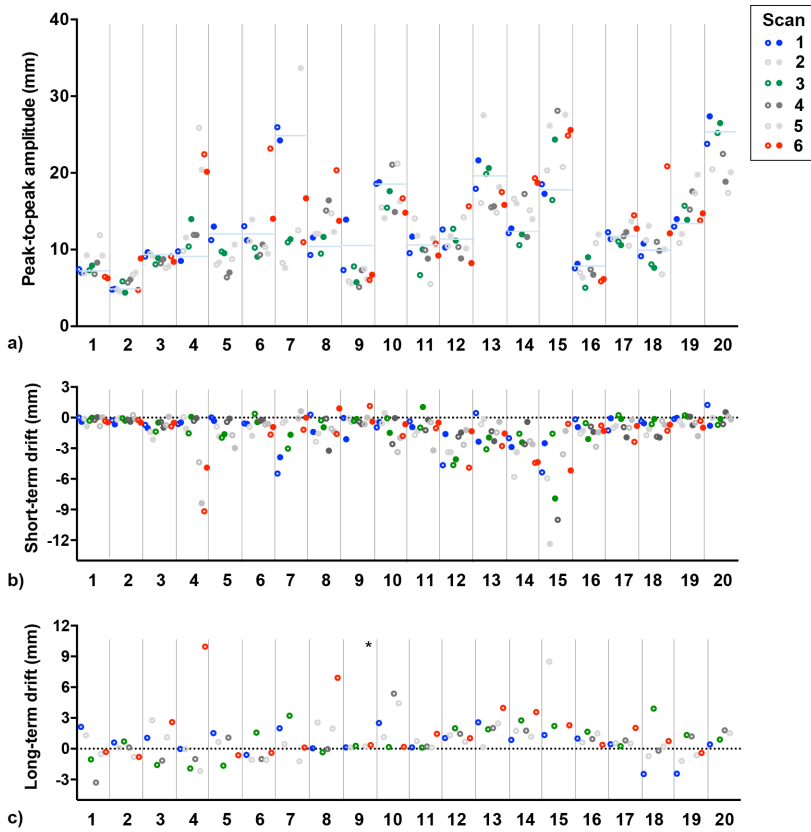
Figure 4. Intra-fraction motion for the six different time points visualized for each patient. For every time point the peak-to-peak cranio-caudal-motion is shown for both scans within the session. The second series is indicated with a closed circle. All patients had a distal tumor, except for patients 1 and 2 (both middle third) and 18 to 20 (gastroesophageal junction). In graph **(A)** the peak-to-peak motion is shown. The blue solid lines indicate the mean peak-to-peak amplitude based on the two baseline scans. The estimated short-term (~ 45 seconds) and long-term drift (~ 10 minutes) are shown in the **(B)** and **(C)**, respectively. In both graphs y=0 is indicated with a dotted line and represents the absence of drift.
* The cine-MRI series of time point 4 for this patient were excluded because of table movement that occurred between the cine-MRI series

Long-term intra-fraction motion

The quantification of shift in CC motion at the start of the drift lines from both the first and second cine-MRI series indicated the presence of drift within the intermediate 10 minutes between the acquisitions of the two series. One time point was excluded due to a table movement between the 2 series. A mean long-term drift (absolute values) of 1.5 mm (SD 1.8) was found, with a maximum long-term drift of 11.6 mm. For each patient the long-term drift is visualized for all 6 time-points in Figure 4c.
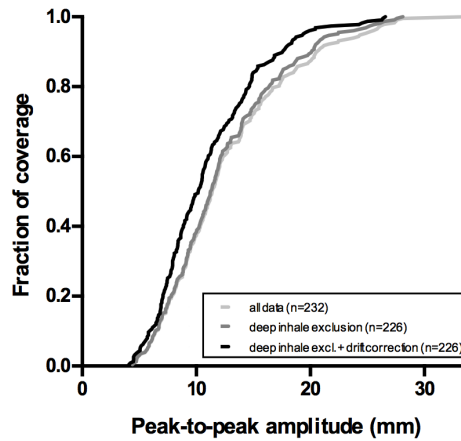
Figure 5. Fraction of scans with a peak-to-peak amplitude lower than the indicated peak-to-peak amplitude, both for the original dataset (n=232), the dataset after exclusion of deep inhales (n=226), and the dataset corrected for tumor drift (n=226). The shift to the left in the lines visualizes the decrease in average peak-to-peak amplitudes after drift correction.

Discussion

In this study, individual intra-fraction motion of esophageal tumors was weekly monitored during the course of nCRT. Interestingly, it was shown that the motion amplitude varied considerably between and within patients. Furthermore, it was found that a baseline scan is not representative to predict tumor motion throughout treatment. Similarly to other studies, it was found that the largest tumor motion occurred in the CC direction.

The large variations in CC amplitudes could be explained by tumor drift within cine-MRI series (short-term drift), but also by a more constant tumor motion pattern that includes a deep inhale, resulting in large peak-to-peak amplitudes. The duration of one fraction of 1.8Gy (approximately 2 minutes) is comparable with the length of one cine-MRI series, which makes the tumor motion found in the cine-MRI series representative for motion that could occur during the delivery of one fraction. Furthermore, long-term drift that occurred within a 10-minute time-interval was quantified, since this could be representative for tumor drift in a time-interval needed for daily dose optimization of the dose plan between positioning of the patient and the actual start of radiation delivery. The radiation dose distributions of patients with large tumor motion have been shown to be influenced by this tumor motion.[21,22] Future work will concentrate on the possible dosimetric consequences of tumor motion for radiotherapy delivery in esophageal cancer and the potential of using personalized motion margins. Furthermore, strategies to mitigate the effect of tumor motion deserve further investigation.

Some previous studies have mentioned pre-treatment identification of regular and irregular breathers.[23] A patient-specific tumor margin for the delivery of radiotherapy could then be determined based on 1 or 2 initial cine-MRI series. However, this is contradicted by the finding of the current study, since large variation in intra-fraction motion is observed in some patients, indicating that an estimation of tumor motion prior to the start of treatment may not represent the actual tumor motion during treatment. The application of fixed margins for esophageal tumors during radiotherapy, e.g. using the well-known 'margin recipe'[24], might not be sufficient when taking the complexity and large variety of tumor motion found in this study into account. However, knowledge of the tumor motion during radiotherapy could enable more conformal dose delivery and individualized treatment strategies. Currently available systems in which tumor tracking during dose delivery is possible are the CyberKnife, using X-ray imaging[25], and the Calypso, using several internal markers for tumor tracking.[26] Furthermore, an integrated MRI and Linac provides the advantages of an MRI system, enabling precise tracking of both tumor and surrounding soft tissues during dose delivery.[12-15] Ultimately, motion margins and consequently unnecessary radiation dose to surrounding organs at risk can be reduced by these approaches.

The conclusion of this study differs from that of Jin et al.[27], who state that motion defined in pre-treatment 4DCT is representative for motion throughout treatment. Furthermore, they stated that 97% of the cases had a motion amplitude of less than 10 mm. While we observed that, after drift correction, only 49% showed a peak-to-peak amplitude of less than 10 mm. Several differences in study setup can explain this. Firstly, both studies report on relatively small patient groups. In our study all patients were male and mainly distal tumors were included, while the study of Jin et al. includes several females and shows a larger variety in tumor locations. Especially the more proximally located tumors exhibit the smallest motion[11] and variability[27], which explains the smaller overall reported variability. Furthermore, tumor motion between males and females could also differ, based on anatomical variations of the thorax or a different breathing pattern.[28,29] Secondly, 4D(CB) CT reconstruction might obscure tumor drift and large inhales, which could be the origin of the larger variability in intra-fraction motion observed in some patients in our MR-based study.

Some limitations apply to our study. First, our study uses temporal 2D datasets, which could lead to the presence of some out-of-plane motion. The analysis was performed on a coronal slices, so out-of-plane motion would be in the AP direction. The average motion observed in this plane is 3.8 mm, which is below the scanned slice thickness of 5 mm. However, the difference in CC motion found between the coronal and sagittal scans hints to the presence of some out-of-plane motion, which could result in an underestimation or overestimation of tumor motion. Second, cine-MRI series were acquired with both arms positioned next

to the body, this could have influenced the reported tumor motion amplitude when compared to the currently used radiotherapy position where both arms are raised above the head. However, the body positioning was consequent throughout all cine-MRI series. Furthermore, this positioning is not expected to influence the main findings of the current study regarding the non-representativeness of a baseline scan for tumor motion throughout treatment and varying motion amplitudes between and within patients.

The size of the motion found in 20 esophageal tumors in 3 different directions presented in this study compares well with previously published work in esophageal cancer.[11,30] Previous published work also described correlations between clinical tumor stage and the mobility of the esophageal tumor. A significantly smaller tumor motion was found in cT4 tumors compared to cT1-T3 tumors, possibly due to the fact that cT4 tumors have an increased adhesion to surrounding tissues.[31] In the current study no statistical analyses were performed to assess the association between tumor location[11] or clinical tumor stage[31] and tumor motion due to the relatively small sample size including mainly distal tumors. In a larger, more heterogeneous cohort, the relation and clinical characteristics could be studied more extensively.

In conclusion, the largest esophageal tumor motion prior to, and throughout the course of nCRT, was found in CC direction, followed by the AP and LR direction using cine-MRI series. Tumor motion in CC direction is highly variable between and within patients during the course of nCRT, as well as within one cine-MRI series (45 seconds) and over a 10-minute interval. It was shown that esophageal tumor motion does not only comprise of respiratory motion, but is also caused by a tumor drift in some patients. The stochastic nature of both deep inhales and tumor drift indicates that real-time tumor motion management during radiotherapy is a prerequisite to safely reduce treatment margins.

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3

Radiation dose and pathological response in oesophageal cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery: a multi-institutional analysis

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Joint first and last authorship.

Abstract

Purpose
To explore whether a higher neoadjuvant radiation dose increases the probability of a pathological complete (pCR) or major (pMR) response in oesophageal cancer patients.

Materials and methods
Between 2000-2017, 1048 patients from four institutions were stratified according to prescribed neoadjuvant radiation doses of 36.0 Gy (13.3%), 40.0 Gy (7.4%), 41.4 Gy (20.1%), 45.0 Gy (25.5%) or 50.4 Gy (33.7%) in 1.8-2.0 Gy fractions. Endpoints were pCR (tumour regression grade (TRG) 1) and pMR (TRG 1+2). Multivariable binary (TRG 1+2 vs. TRG >2) and ordinal (TRG 1 vs. TRG 2 vs. TRG >2) logistic regression analyses were performed, with subgroup analyses according to histology (squamous cell carcinoma (SCC) vs. adenocarcinoma (AC)). Variables entered in the regression model along with neoadjuvant radiation dose were clinical tumour stage (cT), histology, chemotherapy regimen, induction chemotherapy and time from neoadjuvant chemoradiation to surgery.

Results
A pCR was observed in 312 patients (29.8%), of whom 22.7% patients with AC and 49.6% with SCC. No radiation dose response relation was observed for pCR (OR: 1.01, 95% CI: 0.98-1.05 for AC and OR: 1.03, 95% CI: 0.96-1.10 for SCC). A pMR was observed in 597 patients (57.0%); in 53.4% patients with AC and in 67.2% patients with SCC. A higher radiation dose increased the probability of achieving pMR (OR: 1.04, 95% CI: 1.02-1.05). Factors reducing this probability were advanced cT stage (reference = cT1-2; cT3: OR: 0.54, 95% CI: 0.37-0.80; cT4: OR: 0.45, 95% CI: 0.24-0.84), AC histology (reference = SCC; OR: 0.62, 95% CI: 0.44-0.88), the use of non-platinum based chemotherapy in SCC patients (OR: 0.30, 95% CI: 0.10-0.91) and platinum based chemotherapy without induction chemotherapy in patients with AC (OR: 0.56, 95% CI: 0.42-0.76). The radiation dose response relation was confirmed in a subgroup analysis of histologic subtypes (OR: 1.02, 95% CI: 1.01-1.04 for AC and OR: 1.05, 95% CI: 1.02-1.08 for SCC).

Conclusions
Neoadjuvant radiation dose impacts pathological response in terms of pMR in oesophageal cancer patients. No radiation dose response effect was observed for pCR. Further prospective trials are needed to investigate the dose response relation in terms of pCR.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) for locally advanced oesophageal cancer has been shown to improve locoregional control and survival compared to surgery alone in several randomized controlled trials.[1-3] These results have led to the widespread adoption of trimodality therapy as standard of care for locally advanced oesophageal cancer, consisting of preoperative chemotherapy with concurrent radiotherapy followed by oesophagectomy.[4,5] The improvement in survival after trimodality therapy is largely dependent on tumour response to nCRT, which can be assessed by histological examination of the resected oesophagus. Overall, a pathological complete response (pCR), being defined as complete absence of viable tumour cells in the resection specimen, is obtained in 16-40% of patients.[1,3,6] This wide range in pCR rates might be due to considerable heterogeneity in preoperative treatment regimens, with neoadjuvant radiation doses ranging from 36.0 Gy to 50.4 Gy, accompanied by various chemotherapy regimens.[1-3,6] In oesophageal cancer, the use of nCRT mainly aims at pCR. However, it could be argued that patients with a complete and near-complete response might be clustered and described as pathological major response (pMR).[7] This is a common approach for response assessment in rectal cancer patients, especially since the interval between nCRT and surgery can be heterogeneous and might impact response rates.[8-12]

A possible strategy for treatment intensification could be to increase the neoadjuvant radiation dose. However, higher radiation doses to the tumour also lead to higher doses to the surrounding organs at risk (OAR) and have been shown to increase postoperative complication rates.[13-18] On the other hand, the increase in possibilities with proton therapy and the introduction of MRI guided radiation delivery, make it feasible to escalate the radiation dose without increasing the dose to OAR.[19-21] The available studies that assess whether neoadjuvant radiation dose influences tumour response rates in patients with oesophageal cancer are equivocal, and the debate regarding the optimal neoadjuvant radiation dose is still ongoing.[22-25] Therefore, the goal of the current study was to retrospectively explore the hypothesis that a higher neoadjuvant radiation dose could increase pathological tumour response rates in oesophageal cancer patients, in terms of achievement of pCR and pMR.

Materials and methods

Patients
Consecutive patients with locally advanced resectable oesophageal cancer scheduled for and treated with nCRT followed by surgery at four high volume institutes between 2000 and 2017 were included. Patients were stratified according to the prescribed total neoadjuvant radiation dose of 36.0 Gy, 40.0 Gy, 41.4 Gy, 45.0 Gy and 50.4 Gy. Exclusion

criteria were (1) a histologic subtype other than squamous cell carcinoma (SCC) or adenocarcinoma (AC) as based on the resection specimen and in case of a pCR based on the primary tumour biopsy, (2) the presence of distant metastases and (3) treatment with proton radiotherapy. Patients were identified from prospectively maintained databases in the following four university medical centres: University Hospitals Leuven (Belgium), University Medical Center Utrecht (the Netherlands), University of Texas MD Anderson Cancer Center (United States of America) and Ghent University Hospital (Belgium).

All patients underwent an endoscopy with biopsy for histological proof of malignancy and a computed tomography (CT) scan of the chest and abdomen or a ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT (^{18}F-FDG-PET/CT) for staging. Other examinations were performed according to institutional guidelines.

Treatment

Radiotherapy was delivered in fractions of 1.8 Gy or 2.0 Gy by three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT). Delineation of the target volume was according to institutional guidelines. Typically gross target volume (GTV) was based on endoscopy, CT or ^{18}F-FDG-PET/CT and expanded with a 3-4 cm margin in cranio-caudal direction and 0.5-1 cm circumferentially, respecting the anatomic boundaries. The choice of chemotherapy regimen and whether or not induction chemotherapy prior to nCRT was administered, was at the discretion of the treating multidisciplinary team. The patients receiving 36.0 Gy were treated in a single hospital and generally received platinum based chemotherapy without induction therapy. In the single hospital treating patients with 41.4 Gy, only platinum based chemotherapy and no induction therapy was given (as per CROSS trial).[3] One hospital treated patients with both 40.0 Gy and 45.0 Gy and all patients received platinum based chemotherapy, most commonly combined with induction chemotherapy. The fourth hospital treated patients with 45.0 Gy and 50.4 Gy with either a platinum or non-platinum based chemotherapy regimen, and sometimes administered induction chemotherapy.

After nCRT, patients were scheduled for transthoracic or transhiatal surgery with two- or three-field lymphadenectomy, based on the location of the tumour and pathological lymph nodes, as well as the preference of the surgeon.

Outcome measures

Clinical and treatment-related characteristics were acquired from the prospectively collected databases at the four centres. The time from nCRT to surgery was defined as the interval in days between the last day of radiotherapy and the date of surgery. Histologic tumour regression grades (TRG) of the primary tumour were based on histopathological evaluation of the resection specimen by dedicated gastrointestinal pathologists and grouped into three

TRG groups: TRG 1 defined as Mandard 1 or 0.0% viable tumour cells (pCR), TRG 2 defined as Mandard 2 or <10.0% viable tumour cells and TRG >2 defined as Mandard >2 or >10.0% viable tumour cells.[26,27] pMR was defined as TRG 1 and 2 combined.

Overall survival was calculated based from the day of surgery to the date of all-cause death or last day of follow-up.

Statistical analysis

Summary statistics were presented as medians and interquartile range (IQR) for continuous variables, and as frequencies and percentages for categorical variables. To evaluate group differences in patient and treatment variables, the chi-square and ANOVA test were used for categorical and continuous variables, respectively.

The relation between neoadjuvant radiation dose and pathological response was studied in a multivariable binary and ordinal logistic regression analysis. The ordinal logistic regression analysis considered three categories of the dependent variable: TRG >2, TRG 2 and TRG 1 (i.e. pCR). In the multivariable binary logistic regression model, the dependent variable was categorised as TRG 1 and 2 (i.e. pMR) versus TRG >2. Variables to be entered in the regression model along with neoadjuvant radiation dose were based on clinical relevance and literature review of potential confounders: clinical tumour stage (cT), histology, chemotherapy regimen, the use of induction chemotherapy before nCRT, and the time from nCRT to surgery. Furthermore, interactions between histology and (induction) chemotherapy were added to the models when appropriate. Pre-specified subgroup analyses by histology were performed. Patients with missing outcome or covariables were excluded from the analyses.

The Kaplan-Meier method was used to estimate overall survival of pCR and pMR in the entire patient cohort and according to histology.

All analyses were performed with SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patients

A total of 1102 patients were retrieved from the databases. Fifty-four patients (45 patients with AC and 9 patients with SCC) with a missing endpoint or covariable were excluded, resulting in 1048 patients eligible for analyses (Supplementary figure 1). Patients received either 36.0 Gy (139, 13.3%), 40.0 Gy (78, 7.4%), 41.4 Gy (211, 20.1%), 45.0 Gy (267, 25.5%) or 50.4 Gy (353, 33.7%). Patient, tumour and treatment-related characteristics of the patient cohort are presented in Table 1. The majority of patients were male (837, 79.9%) and the median age was 62 years (IQR 55-68 years). The predominant histologic tumour type was

AC (774, 73.9%) and cT3 was the most common tumour stage (857, 81.8%). Most patients had positive lymph nodes upon clinical staging (796, 76.0%). The patients treated with 36.0 Gy received platinum based chemotherapy (except one) without induction therapy (except one). In one hospital treating patients with 45.0 Gy and 50.4 Gy, a non-platinum based chemotherapy regimen was administered in half of the cases and induction chemotherapy was given in 38.3% of all patients.

Table 1. Baseline characteristics of the study population

Characteristic	Total n = 1048 (100%)	36.0 Gy n = 139 (13.3%)	40.0 Gy n = 78 (7.4%)	41.4 Gy n = 211 (20.1%)	45.0 Gy n = 267 (25.5%)	50.4 Gy n = 353 (33.7%)	p-value
Age at diagnosis, years (median (IQR))	62 (55-68)	62 (55-69)	60 (53-66)	67 (60-71)	62 (55-69)	60 (52-65)	<0.001
Sex							
Male	837 (79.9)	112 (80.6)	58 (74.4)	160 (75.8)	196 (73.4)	311 (88.1)	<0.001
Female	211 (20.1)	27 (19.4)	20 (25.6)	51 (24.2)	71 (26.6)	42 (11.9)	
Chemotherapy regimen							
Platinum based	852 (81.3)	138 (99.3)	78 (100)	211 (100)	246 (92.1)	179 (50.7)	<0.001
Non-platinum based	196 (18.7)	1 (0.7)	0 (0.0)	0 (0.0)	21 (7.9)	174 (49.3)	
Induction chemotherapy							
Yes	420 (40.1)	1 (0.7)	61 (78.2)	0 (0.0)	235 (88.0)	123 (34.8)	<0.001
No	628 (59.9)	138 (99.3)	17 (21.8)	211 (100)	32 (12.0)	230 (65.2)	
Days end radiation until surgery (median (IQR))	53 (44-64)	34 (29-38)	55 (47-64)	62 (50-75)	55 (47-64)	57 (47-78)	<0.001
Clinical T status							
T1	8 (0.8)	2 (1.4)	0 (0.0)	3 (1.4)	1 (0.4)	2 (0.6)	<0.001
T2	126 (12.0)	15 (10.8)	6 (7.7)	36 (17.1)	31 (11.6)	38 (10.8)	
T3	857 (81.8)	117 (84.2)	46 (59.0)	169 (80.1)	218 (81.6)	307 (87.0)	
T4	57 (5.4)	5 (3.6)	26 (33.3)	3 (1.4)	17 (6.4)	6 (1.7)	
Clinical N status							
N0	244 (23.3)	20 (14.4)	4 (5.1)	59 (28.0)	37 (13.9)	124 (35.1)	<0.001
N+	796 (76.0)	113 (81.3)	73 (93.6)	152 (72.0)	230 (86.1)	228 (64.6)	
Nx	8 (0.8)	6 (4.3)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	
Histology							
Squamous cell carcinoma	274 (26.1)	52 (37.4)	44 (56.4)	66 (31.3)	81 (30.3)	31 (8.8)	<0.001
Adenocarcinoma	774 (73.9)	87 (62.6)	34 (43.6)	145 (68.7)	186 (69.7)	322 (91.2)	
Pathologic response							
TRG 1	312 (29.8)	37 (26.6)	26 (33.3)	63 (29.9)	89 (33.3)	97 (27.5)	NA
TRG 2	285 (27.2)	35 (25.2)	20 (25.6)	45 (21.3)	83 (31.1)	102 (28.9)	
TRG >2	451 (43.0)	67 (48.2)	32 (41.0)	103 (48.8)	95 (35.6)	154 (43.6)	

IQR interquartile range, *TRG* tumour regression grade, *NA* not applicable (appropriate analyses reported elsewhere)
Values are numbers of patients, with column-based percentages in parentheses unless stated otherwise.

Pathologic complete response

A pCR was demonstrated in 312 patients (29.8%), of which 176 of 774 patients (22.7%) with AC and 136 of 274 patients (49.6%) with SCC. A dose response diagram for the endpoint TRG 1 (pCR) vs. TRG 2 vs. TRG >2 is presented in Figure 1.

Multivariable ordinal logistic regression analysis with TRG >2, TRG 2 and TRG 1 as outcome categories demonstrated no significant impact of total neoadjuvant radiation dose for both histologic subtypes (per additional Gy: OR 1.01, 95% CI 0.98-1.05, p=0.403 for AC and OR 1.03, 95% CI 0.96-1.10, p=0.402 for SCC) (Table 2). In the patients with AC, advanced tumour stage (with cT1-2 as reference; cT3-4: OR 0.53, 95% CI 0.36-0.78, p=0.002) and the use of platinum based chemotherapy without induction chemotherapy (OR 0.56, 95% CI 0.41-0.77, p<0.001) reduced the odds of pCR. For patients with SCC, only an advanced tumour stage reduced the odds of pCR (with cT1-2 as reference; cT3-4: OR 0.45, 95% CI 0.12-1.11, p=0.030).

Pathologic major response

A pMR was obtained in 597 of 1048 patients (57.0%). In binary multivariable logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.04, 95% CI 1.02-1.05, p<0.001). Factors that reduced these odds were a higher tumour stage (with cT1-2 as reference; cT3: OR 0.54, 95% CI 0.37-0.80, p=0.002 and cT4: OR 0.45, 95% CI 0.24-0.84, p=0.013) as well as AC histology (OR 0.62, 95% CI 0.44-0.88, p=0.008). The use of non-platinum based
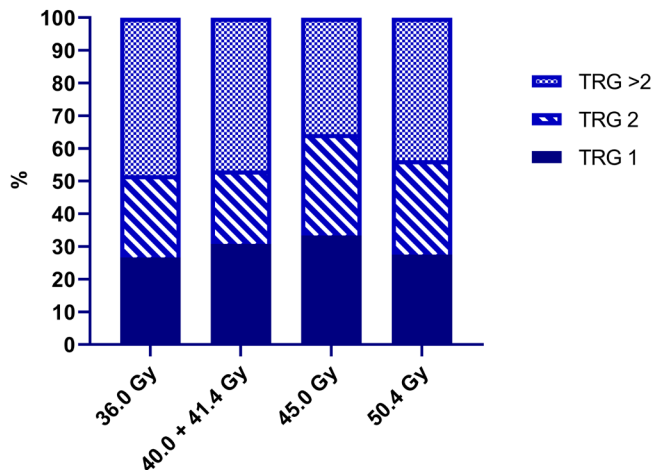

Figure 1. Dose response diagram for tumour regression grades (TRG) within the entire patient cohort

chemotherapy in patients with SCC decreased the odds of pMR (OR 0.30, 95% CI: 0.10-0.91, p=0.034). The use of platinum based chemotherapy without induction chemotherapy in patients with AC had a negative effect on pMR (OR 0.56, 95% CI 0.42-0.76, p<0.001) (Table 3).

Subgroup analyses for pathologic major response according to histology

In patients with AC, a pMR was achieved in 413 of 774 patients (53.4%). In binary multivariable logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.02, 95% CI 1.01-1.04, p<0.001). Factors reducing the odds were advanced tumour stage (with cT1-2 as reference; cT3: OR 0.59, 95% CI 0.38-0.91, p=0.016 and cT4: OR 0.56, 95% CI 0.23-1.36, p=0.199) and the use of platinum based chemotherapy without induction chemotherapy (OR 0.54, 95% CI 0.41-0.72, p<0.001) (Table 3).

For SCC, 184 of 274 patients (67.2%) achieved a pMR. In multivariable binary logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.05, 95% CI 1.02-1.08, p=0.001). Factors that reduced these odds were higher tumour stage (with cT1-2 as reference; cT3: OR 0.32, 95% CI 0.12-0.82, p=0.018 and cT4: OR 0.23, 95% CI 0.07-0.71, p=0.011) and the use of non-platinum based chemotherapy (OR 0.27, 95% CI 0.09-0.83, p=0.022).

Table 2. Multivariable ordinal logistic regression analysis with three pathological response groups as outcome variable (TRG >2, TRG 2 and TRG 1 (pCR)), according to histologic subgroups

Adenocarcinoma (n=774)	OR (95% CI)	p-value
Total neoadjuvant radiation dose per Gy	1.01 (0.98-1.05)	0.403
Tumour stage (cT1-2 as reference)*		
cT3-4	0.53 (0.36-0.78)	**0.002**
Platinum based chemotherapy without induction chemotherapy	0.56 (0.41-0.77)	**<0.001**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99-1.01)	0.812
Squamous cell carcinoma (n=274)	**OR (95% CI)**	**p-value**
Total neoadjuvant radiation dose per Gy	1.03 (0.96-1.10)	0.402
Tumour stage (cT1-2 as reference)*		
cT3-4	0.45 (0.12-1.11)	**0.030**
Non-platinum based chemotherapy	0.36 (0.41-0.77)	0.076
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99-1.01)	0.878

CI confidence interval, *OR* odds ratio, *pCR* pathological complete response, *TRG* tumour regression grade
* Clinical tumour stages were combined for these subgroups analyses because of small patient numbers per stage. The Test of Parallel Lines had a p-value of 0.051 (degrees of freedom (df)=4, adenocarcinoma) and 0.386 (df=4, squamous cell carcinoma) respectively.

Table 3. Multivariable logistic regression analysis with pathological major response (pMR) as outcome variable in the entire patient cohort and according to histologic subgroups

Entire cohort (n=1048)	OR (95% CI)	p-value
Total neoadjuvant radiation dose per Gy	1.04 (1.02-1.05)	**<0.001**
Adenocarcinoma (squamous cell carcinoma as reference)	0.62 (0.44-0.88)	**0.008**
Tumour stage (cT1-2 as reference)*		
cT3	0.54 (0.37-0.80)	**0.002**
cT4	0.45 (0.24-0.84)	**0.013**
Interaction between adenocarcinoma and platinum based chemotherapy without induction chemotherapy	0.56 (0.42-0.76)	**<0.001**
Interaction between squamous cell carcinoma and non-platinum based chemotherapy	0.30 (0.10-0.91)	**0.034**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99-1.00)	0.241
Adenocarcinoma (n=774)	**OR (95% CI)**	**p-value**
Total neoadjuvant radiation dose per Gy	1.02 (1.01-1.04)	**<0.001**
Tumour stage (cT1-2 as reference)*		
cT3	0.59 (0.38-0.91)	**0.016**
cT4	0.56 (0.23-1.36)	0.199
Platinum based chemotherapy without induction chemotherapy	0.54 (0.41-0.72)	**<0.001**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99-1.00)	0.291
Squamous cell carcinoma (n=274)	**OR (95% CI)**	**p-value**
Total neoadjuvant radiation dose per Gy	1.05 (1.02-1.08)	**0.001**
Tumour stage (cT1-2 as reference)*		
cT3	0.32 (0.12-0.82)	**0.018**
cT4	0.23 (0.07-0.71)	**0.011**
Non-platinum based chemotherapy	0.27 (0.09-0.83)	**0.022**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.98-1.01)	0.674

CI confidence interval, *OR* odds ratio, *pMR* pathological major response
* cT1 and cT2 were combined as a reference category, since only few patients had a cT1 stage.
The Hosmer-Lemeshow goodness of fit test had a p-value of 0.399 (degrees of freedom (df)=8, entire patient cohort), 0.754 (df=8, adenocarcinoma) and 0.276 (df=8, squamous cell carcinoma) respectively.

4

Survival analysis

Median follow-up time of the patients was 25.1 months (IQR 11.0-54.7 months). The median OS of patients with a pCR, TRG 2 and TRG >2 was 78 months, 46 months and 28 months, respectively (Supplementary Material 2). For patients with an AC, the median OS was 90 months for pCR, 50 months for TRG 2 and 30 months TRG >2. For patients with an SCC, the median OS was 67 months for pCR, 38 months for TRG 2 and 16 months TRG >2 (Supplementary Material 2).

The median OS of patients with a pMR and TRG >2 was 61 months and 28 months, respectively (Figure 2). For patients with an AC, the median OS was 64 months for pMR and 30 months TRG >2. For patients with an SCC patients, the median OS was 55 months for pMR and 16 months TRG >2 (Figure 2).
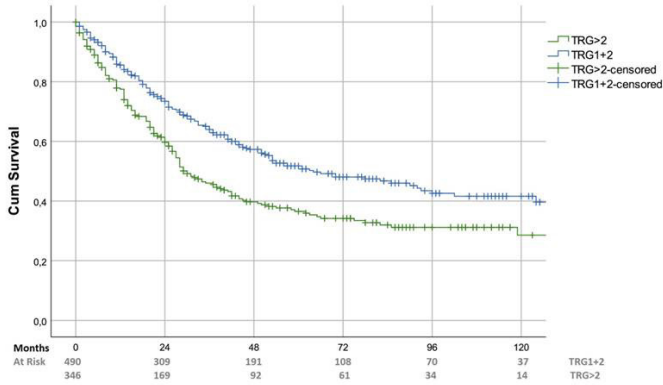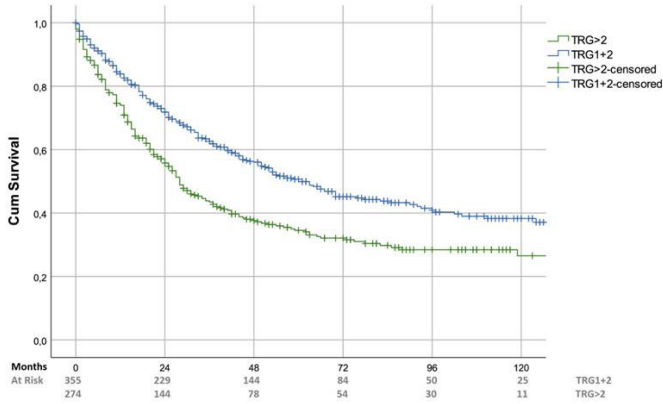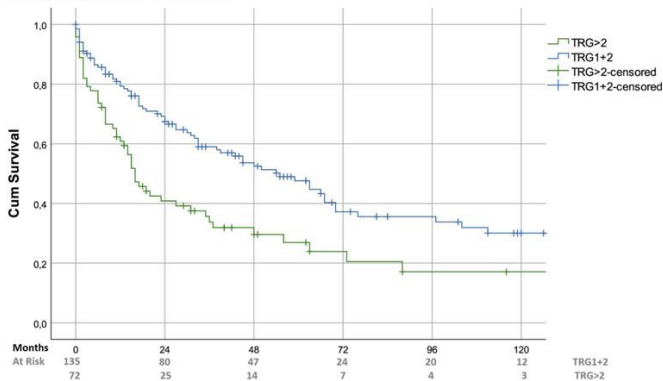
Figure 2. Overall survival curves of tumour regression grades (TRG) 1+2 (pathologic major response; pMR, blue curve) vs. TRG >2 (green curve) in the entire patient cohort (**A**) and according to histologic subgroups (adenocarcinoma: **B**, squamous cell carcinoma: **C**)

Discussion

In this study, we analysed the pathological response rate after nCRT followed by surgery in 1048 patients with oesophageal cancer from four high volume institutes. The balance between the pathological response and the toxicity of neoadjuvant therapy emphasizes the need to explore a dose response relationship, especially in the era of an increasing use of a wait-and-see policy in clinical complete responders. Some evidence of a dose response relation has been described in observational studies.[22,25] To our knowledge, no randomised controlled trials have been performed comparing different neoadjuvant radiotherapy schedules for patients with oesophageal cancer. Our study did not observe a dose response relation for pCR (TRG 1) in multivariable ordinal regression analyses. However, a dose response relation was observed for radiation dose and pMR (TRG 1+2), where the neoadjuvant radiation dose, besides the tumour stage, histology, induction chemotherapy and the chemotherapy regimen, increased the odds of a pMR. As the cohort of patients with SCC was rather small compared to that of the patients with AC, especially in the subgroup of non-platinum based chemotherapy and in the group of patients receiving 50.4 Gy, the effect of dose in patients with SCC should be interpreted with caution.

Next to the neoadjuvant radiation dose, the impact of the concurrent chemotherapy regimen and the use of induction chemotherapy was studied. A non-platinum based chemotherapy was less effective to achieve a pMR in patients with SCC. When induction chemotherapy was administered in patients with AC, there was an improvement in pMR only when platinum based chemotherapy was used concomitantly. In literature, limited data are available on the use of non-platinum based chemotherapy and the pathological response rate in patients with SCC and AC separately in the preoperative setting in oesophageal cancer patients.[28,29] The observed differences in chemo- and radiotherapy sensitivity underline the necessity for researching individualized treatment regimens for both histologic subgroups.

Next to pCR, pMR was chosen as secondary outcome variable for several reasons. First, the interval between the last day of radiotherapy and the surgery might affect the degree of pathological response, i.e. a shorter interval between nCRT and surgery might underestimate the presence of a pathological response.[30] To eliminate this bias, the interval between nCRT and surgery was taken into account in the multivariable analyses, and pathological complete and near-complete responders were grouped as patients with pMR in a secondary analysis as well. Second, the benefit in overall survival and progression free survival has been suggested to be comparable between patients with a pCR and those with a low percentage of residual tumour cells in a meta-analysis.[8] Lastly, a similar strategy has been applied in other cancer types, such as rectal cancer, where both clinical complete and near-complete responders are considered eligible for an organ-preservation strategy.[9.]

In our study, reaching a pMR or pCR, compared to TRG >2, was as expected associated with a survival advantage, both in the entire patient cohort as in the subgroups according to histology.[8,31] Despite the large patient cohort, we acknowledge that these analyses were subject to an unbalanced distribution of confounders, related to clinical and treatment-related variables.

Potential limitations of this study include its retrospective nature. Additionally, the tumour regression grade was evaluated by centre-specific pathologists and only evaluated the regression grade of the primary tumour and not of the lymph nodes. As a consequence, persistent disease only at the nodal level was possible.[32-34] Since the lack of adequate tumour regression grade systems for nodes after preoperative treatment and the relatively low percentage of patients in our study with an ypT0N+, the current study focussed on the primary tumour. However, in order to investigate the effect of increased neoadjuvant radiation dose on survival, the response of the primary tumour should be combined with the pathological nodal stage, since the latter is one of the most important determinants of overall survival after nCRT followed by surgery.[8,35,36] Another limitation involves that all patients scheduled for and actually treated with nCRT followed by surgery (i.e. preoperative intent) were included in the analysis. As such, there might have been a selection bias by excluding patients who started nCRT but did not proceed to surgery, e.g. patients with a clinical complete response in whom an active surveillance strategy was applied. On the other hand, in a few patients surgery was delayed, due to prolonged treatment recovery from nCRT and observation. Additionally, toxicity data were not available and further studies are warranted to investigate the influence of nCRT on toxicity and postoperative complications. Lastly, we acknowledge that the treatment regimen, i.e. radiation dose and concurrent chemotherapy regimen, was directly linked to the centre, which might have resulted in residual confounding. Despite the aforementioned limitations, major strengths of this study include that this is a large multi-centre study, based on high-quality prospectively collected data. In contrast to previous studies, information on the concurrent chemotherapy regimen and on the use of induction chemotherapy was available, which is important in analysing pathological response rates.
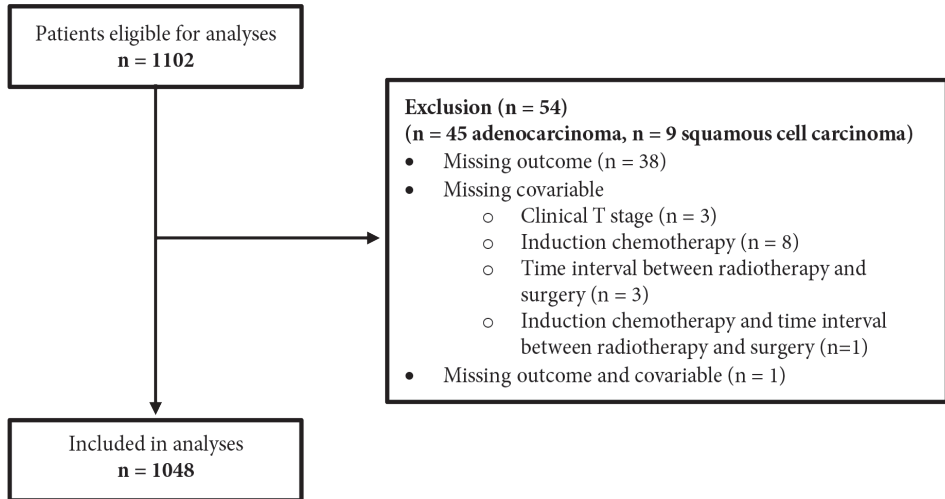
In conclusion, this study demonstrated that the total neoadjuvant radiation dose had an impact on pathological response in terms of pMR in patients with oesophageal cancer. However, no radiation dose response effect was observed for pCR. Further prospective trials are needed to investigate the dose response relation in terms of pCR.
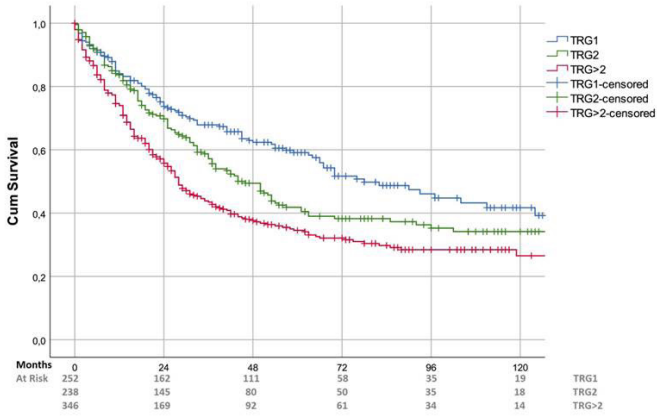
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SUPPLEMENTARY MATERIAL

Supplementary figure 1. Consort diagram of the study

A. Entire cohort

Months	0	24	48	72	96	120	
At Risk	252	162	111	58	35	19	TRG1
	238	145	80	50	35	18	TRG2
	346	169	92	61	34	14	TRG>2

B. Adenocarcinoma

Months	0	24	48	72	96	120	
At Risk	154	104	74	37	17	9	TRG1
	201	125	70	47	33	16	TRG2
	274	144	78	54	30	11	TRG>2

C. Squamous cell carcinoma

Months	0	24	48	72	96	120	
At Risk	98	58	37	21	18	10	TRG1
	37	21	10	3	2	2	TRG2
	72	25	14	7	4	3	TRG>2
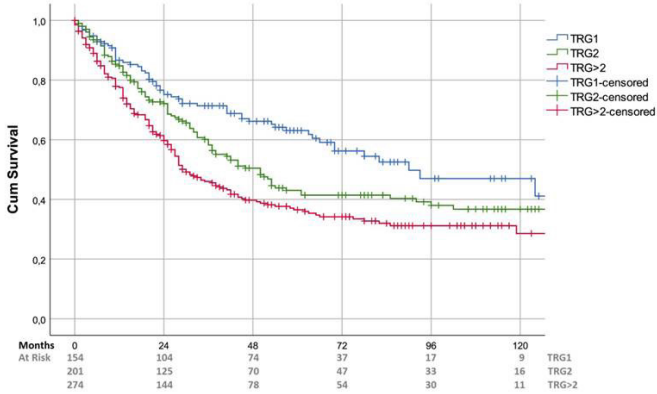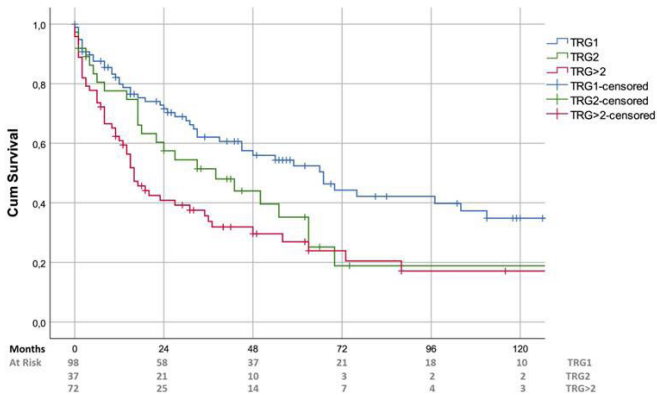
Supplementary figure 2. Overall survival curves of tumour regression grade (TRG) 1 (pathologic complete response; pCR, blue curve) vs. TRG 2 (green curve) vs. TRG >2 (red curve) in the entire patient cohort (**A**) and according to histologic subgroups (adenocarcinoma: **B**, squamous cell carcinoma: **C**).

Treatment response assessment

Preoperative prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal cancer using ^{18}F-FDG PET/CT and DW-MRI: a prospective multicenter study

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Abstract

Background

Accurate preoperative prediction of pathologic response to neoadjuvant chemoradio-therapy (nCRT) in esophageal cancer patients could enable to forgo esophagectomy in patients with a pathologic complete response (pCR). This study aimed to evaluate the individual and combined value of ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET/CT) and diffusion-weighted magnetic resonance imaging (DW-MRI) during and after nCRT to predict pathologic response in esophageal cancer patients.

Methods

In this multicenter prospective study, patients scheduled to receive nCRT followed by esophagectomy for esophageal cancer underwent ^{18}F-FDG PET/CT and DW-MRI scanning prior to start of nCRT, during nCRT, and before esophagectomy. Response to nCRT was based on histopathological evaluation of the resection specimen. Relative changes in ^{18}F-FDG PET/CT and DW-MRI parameters were compared between patients with pCR and non-pCR groups. Multivariable Ridge regression analyses with bootstrapped c-indices were performed to evaluate the individual and combined value of ^{18}F-FDG PET/CT and DW-MRI.

Results

pCR was found in 26.1% of 69 patients. Relative changes in ^{18}F-FDG PET/CT parameters *after* nCRT ($\Delta SUV_{mean,post}$ p=0.016, and ΔTLG_{post} p=0.024), as well as changes in DW-MRI parameters *during* nCRT (ΔADC_{during} p=0.008) were significantly different between pCR and non-pCR. A c-statistic of 0.84 was obtained for a model with ΔADC_{during}, $\Delta SUV_{mean,post}$ and histology in classifying patients as pCR (versus 0.82 for ΔADC_{during} and 0.79 for $\Delta SUV_{mean,post}$ alone).

Conclusions

Changes on ^{18}F-FDG PET/CT after nCRT and early changes on DW-MRI during nCRT can help identify pCR to nCRT in esophageal cancer. Moreover, ^{18}F-FDG PET/CT and DW-MRI might be of complementary value in the assessment of pCR.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is the preferred treatment with curative intent for patients with locally advanced esophageal cancer.[1] Through tumor downsizing and downstaging, nCRT improves locoregional control and overall survival rates compared to surgery alone.[2–4] Many studies have reported that the degree of tumor regression in response to nCRT is directly related to long-term survival, with pathologic complete responders having the most favorable long-term prognosis.[3,5] The absence of viable tumor cells at the site of the primary tumor in pathologic complete responders raises the question whether a surgical resection is of benefit for patients who might have already been cured locoregionally by nCRT alone.[6] Accurate prediction of pathologic complete response (pCR) before surgery could potentially allow patients to forgo surgery and would enable researchers to study the feasibility and outcome of an organ-preserving strategy after chemoradiotherapy. Conversely, patients with a poor response to nCRT are likely to benefit less or not at all from nCRT, but are exposed to its side-effects. A reliable identification of poor responders during nCRT may thus be also beneficial, as ineffective therapy could be stopped and/or alternative treatment strategies (e.g. additional neoadjuvant treatment or upfront surgery) could be explored.

Unfortunately, most studied modalities – including endoscopic biopsy, endoscopic ultrasonography (EUS) and computed tomography (CT) – yield unsatisfactory results for the evaluation of tumor response to nCRT.[7–11] Metabolic and functional imaging modalities such as ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET/CT) and diffusion-weighted magnetic resonance imaging (DW-MRI) may be more promising because they allow biological and microstructural characterization of tumors and visualization of treatment-induced changes before volumetric changes become apparent.[9,12–18] However, the discriminatory ability of ^{18}F-FDG PET/CT alone has previously shown in a multitude of studies to be insufficient to guide clinical decision-making.[14,19,20] The performance of DW-MRI and the quantitative apparent diffusion coefficient (ADC) are promising in predicting response to nCRT although they have been demonstrated only in two small single-center pilot studies.[16,17]

A multimodality imaging approach, in comparison to that of a single-modality, may provide complementary value for predicting pathologic response, with the ultimate goal of optimally guiding individualized treatment decision-making. Therefore, the aim of this prospective multicenter study was to evaluate the individual and combined value of ^{18}F-FDG PET/CT and DW-MRI during and after nCRT to predict pathologic response in patients who undergo nCRT for esophageal cancer, as well as to validate these findings for the prediction of survival.

Methods

Three high volume institutions participated in this multicenter prospective study including the University Medical Center Utrecht (UMC Utrecht), the Netherlands Cancer Institute (NKI-AVL) and the University of Texas MD Anderson Cancer Center (MDACC). The study has been approved by the institutional review board of each institution separately, and all patients provided their written informed consent. The study was registered with ClinicalTrials.gov, number NCT02125448.

Study population

Patients presenting at any of the 3 participating institutions from October 2013 to July 2017 with newly diagnosed biopsy-proven esophageal cancer who were scheduled to receive nCRT followed by surgery were eligible for inclusion. Exclusion criteria are outlined in the Supplementary Methods. The results of first 20 of the 26 included patients from the MDACC have been published previously.[17]

Treatment protocol

At the UMC Utrecht and NKI-AVL, the neoadjuvant treatment regimen consisted of carboplatin/paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy).[4] At the MDACC, the regimen consisted of 5-fluorouracil with either platinum or taxane-based chemotherapy and concurrent radiotherapy (50.4 Gy in 28 fractions of 1.8 Gy). All patients were treated with an intensity-modulated radiation therapy (IMRT) technique. At a median of 8 weeks (interquartile range [IQR]: 7-10 weeks) after completion of nCRT, patients underwent a transhiatal or transthoracic esophagectomy with two-field lymphadenectomy and gastric conduit reconstruction with either cervical or intrathoracic anastomosis, depending on patient characteristics and local preference.

Histopathological assessment

Histopathological tumor regression of the surgical resection specimen was assessed by specialized gastrointestinal pathologists who were blinded for the results of the ^{18}F-FDG PET/CT and DW-MRI scans. Patients were staged in accordance with the 7th edition of the Union for International Cancer Control (UICC).[21] The following tumor regression groups were scored: absence of residual cancer cells (TRG 1), 1-10% residual cancer cells (TRG 2), 10-50% residual cancer cells (TRG 3) and >50% residual cancer cells (TRG 4).[22]

Image acquisition

Patients underwent ^{18}F-FDG PET/CT scanning at 3 time points: within a median of 3 weeks (IQR: 2 - 4 weeks) before nCRT, during nCRT at a median of 13 days (IQR: 10 - 15 days)

after initiation of nCRT, and 5 weeks (IQR: 4.5 - 7 weeks) after completion of nCRT and before surgery (median: 14 days [IQR: 9 – 32 days] between ^{18}F-FDG PET/CT scan and surgery).

Patients underwent DW-MRI scanning using 3 different b-values (b = 0, 200 and 800 s/mm^2) at the same 3 time points as the ^{18}F-FDG PET/CT scans. Only the baseline DW-MRI scan was generally not performed on the exact same day as the baseline ^{18}F-FDG PET/CT scan, since the latter was part of the diagnostic work-up and the DW-MRI scan was acquired after patients were included in the study. The baseline DW-MRI scan was in all cases acquired within 2 weeks (median: 5 days, IQR: 1 – 6 days) before nCRT. Detailed image acquisition parameters are presented in the Supplementary Methods.

Image analysis

Details on the ^{18}F-FDG PET/CT and DW-MRI tumor delineation methodology are included in the Supplementary Methods. At each of the 3 time points, the following 4 quantitative metrics were extracted from the ^{18}F-FDG PET/CT primary tumor delineations: mean and maximum standardized uptake value (SUV_{mean}, SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) calculated as the product of MTV and SUV_{mean}.[23] From the DW-MRI primary tumor delineations, the mean ADC values were extracted from the ADC map. The relative changes in percent (Δ%) of these ^{18}F-FDG PET/CT and DW-MRI parameters between baseline scans and the scans during and after nCRT were calculated and considered as possible predictors in the analysis based on prior knowledge (i.e. ΔADC, ΔSUV_{mean}, ΔSUV_{max} and ΔTLG).[16,17,20,24–27]

Statistical analysis

The relative changes of the ^{18}F-FDG PET/CT and DW-MRI parameters were compared between patients with pCR (TRG 1) and non-pCR (TRG 2-4), and between good responders (TRG 1-2, GR) and poor responders (TRG 3-4, non-GR) to validate findings of previous pilot-studies using the Mann-Whitney U test with Benjamin-Hochberg corrections.[16,17,20,24–26,28,29] The ability of single modality ^{18}F-FDG PET/CT and DW-MRI parameters to discriminate between different pathologic response groups was quantified using the area under the receiver operating characteristic curve (c-statistic). The complementary value of ^{18}F-FDG PET/CT and DW-MRI parameters, in addition to histopathological tumor type which known to impact pathologic response to nCRT, was assessed using multivariable penalized Ridge regression models to reduce model overfitting in a situation with few events per variable.[30] The best model for pCR prediction was validated for the prediction of overall survival (OS) and disease free survival (DFS) using multivariable Cox regression analysis. Detailed statistical methods are presented in the Supplementary Methods.
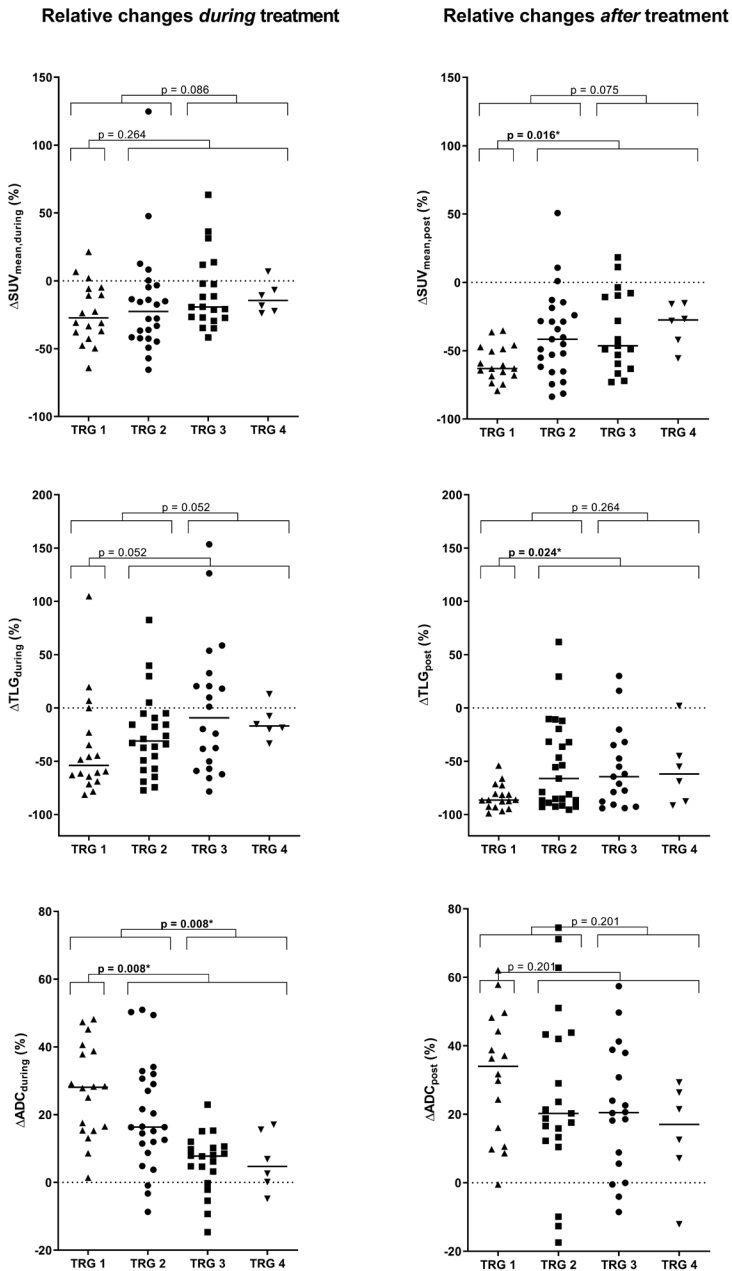
Figure 1. Relative changes in ^{18}F-FDG PET/CT and DW-MRI parameters during and after neoadjuvant chemoradiotherapy in all patients, categorized by histopathologic tumor regression grades (TRG). The solid horizontal lines represent group medians.

Significant differences between the groups based on the Mann-Whitney U test followed by Benjamini-Hochberg adjustment are marked with an asterisk (*).

Results

Study population

Between October 2013 and July 2017, a total of 82 consecutive patients with newly diagnosed esophageal cancer who underwent standard diagnostic work-up signed informed consent. A total of 13 patients were excluded from the analysis (withdrawal from study participation [n=4], unexpected distant metastatic disease [n=3], no tumor signal on the baseline ^{18}F-FDG PET/CT or DW-MRI [n=3], small tumor volume [<2ml, n=2] and refusal of surgery [n=1]). The remaining 69 patients, with a total of 203 ^{18}F-FDG PET/CT scans and 199 DW-MRI scans, were eligible for analysis (Supplementary Figure 1).

Patients had a mean age of 61.0 years (SD ± 9.2 years), and 88.4% (n=61) were male. Histologic tumor types included adenocarcinoma (n=57, 82.6%), squamous cell carcinoma (n=11, 15.9%) or undifferentiated large cell carcinoma type (n=1, 1.4%). Histopathological assessment of the surgical resection specimen demonstrated pCR (i.e. TRG 1) in 18 patients (26.1%), and GR (i.e. TRG 1-2) in 43 patients (62.3%) after nCRT (see also Supplementary Table 1). Patients with a squamous cell carcinoma had a significantly higher probability of pCR and GR compared to patients with adenocarcinoma (Table 1). No significant differences were observed in clinical T stages, nCRT regimens or time intervals from nCRT to surgery between patients with pCR and non-pCR, or between patients with GR and non-GR (Table 1). Detailed patient and tumor characteristics are outlined in Table 1.

Relative changes in ^{18}F-FDG PET/CT and DW-MRI parameters

The relative change in tumor SUV_{mean}, SUV_{max}, TLG and ADC_{mean} during and after nCRT for pCR and GR patients are presented in Table 2 and illustrated in Figure 1. In Figure 2 ^{18}F-FDG PET/CT and MRI scans of a patient with pCR are presented.

The changes in SUV_{mean}, SUV_{max} and TLG from baseline ^{18}F-FDG PET/CT scans to scans acquired during nCRT were not significantly different between patients with pCR versus non-pCR (Table 2). Changes in SUV_{mean} and TLG from baseline ^{18}F-FDG PET/CT scans to scans acquired after completion of nCRT, however, were significantly different between pCR and non-pCR ($\Delta SUV_{mean,post}$ [median, IQR]: -63% [-68%, -49%] for pCR versus -42% [-58%, -16%] for non-pCR, p = 0.016, and ΔTLG_{post} [median, IQR]: -86% [-93%, -81%] for pCR versus -65% [-88%, -32%] for non-pCR, p = 0.024). Regarding GR, none of the changes in ^{18}F-FDG PET/CT parameters from baseline to either during or after completion of nCRT were significantly different between GR and non-GR (Table 2).

The relative increase in tumor ADC from baseline DW-MRI scans to scans acquired during nCRT (ΔADC_{during}) was significantly associated with pCR (median, IQR: 28% [15%, 39%] for pCR versus 11% [4%, 17%] for non-pCR, p = 0.008). In contrast, relative changes in ADC from baseline to scans after completion of nCRT (ΔADC_{post}) were not significantly

Table 1. Clinical characteristics of the study population and univariable analyses between predetermined clinical predictors and response groups.

Characteristics	All n (%)	pCR (n=18) n (%)	non-pCR (n=51) n (%)	p-value	GR (n=43) n (%)	non-GR (n=26) n (%)	p-value
Age at diagnosis, in years (mean ± SD)	61.0 ± 9.2	60.1 ± 8.8	61.4 ± 9.4	NA	61.1 ± 9.4	60.9 ± 9.0	NA
Sex				NA			NA
Male	61 (88)	3 (17)	5 (10)		5 (12)	3 (12)	
Female	8 (12)	15 (83)	46 (90)		38 (88)	23 (88)	
BMI, in kg/m² (mean ± SD)	25.7 ± 3.8	24.7 ± 5.2	26.1 ± 3.1	NA	25.2 ± 4.2	26.7 ± 2.8	NA
WHO performance status at diagnosis				NA			NA
0	27 (39)	5 (28)	22 (43)		18 (42)	9 (35)	
1	40 (58)	12 (67)	28 (55)		24 (56)	16 (62)	
2	2 (3)	1 (6)	1 (2)		1 (2)	1 (4)	
Tumor location				NA			NA
Proximal esophagus	1 (1)	0 (0)	1 (2)		1 (2)	0 (0)	
Middle esophagus	9 (13)	5 (28)	4 (8)		8 (19)	1 (4)	
Distal esophagus	40 (58)	6 (33)	34 (67)		22 (51)	18 (69)	
Gastroesophageal junction	19 (28)	7 (39)	12 (24)		12 (28)	7 (27)	
Clinical T status*				0.233			0.698
T2	9 (13)	2 (11)	7 (14)		6 (14)	3 (12)	
T3	59 (86)	15 (83)	44 (86)		36 (84)	23 (88)	
T4	1 (1)	1 (6)	0 (0)		1 (2)	0 (0)	
Clinical N status*				NA			NA
N0	23 (33)	6 (33)	17 (33)		15 (35)	8 (31)	
N1	26 (38)	5 (28)	21 (41)		12 (28)	14 (54)	
N2	18 (26)	7 (39)	11 (22)		15 (35)	3 (12)	
N3	2 (3)	0 (0)	2 (4)		1 (2)	1 (4)	
Histology				0.001			0.069
Adenocarcinoma	57 (83)	10 (56)	47 (92)		32 (74)	25 (96)	
Squamous cell carcinoma	11 (16)	7 (39)	4 (8)		10 (23)	1 (4)	
Undifferentiated large cell carcinoma	1 (1)	1 (6)	0 (0)		1 (2)	0 (0)	
Tumor regression grade				NA			NA
TRG 1 (pCR)	18 (26)	18 (100)	NA		18 (42)	NA	
TRG 2	25 (36)	NA	25 (49)		25 (58)	NA	
TRG 3	20 (29)	NA	20 (39)		NA	20 (77)	
TRG 4	6 (9)	NA	6 (12)		NA	6 (23)	
Neoadjuvant chemoradiotherapy regimen				0.902			0.357
Carboplatin/paclitaxel + 41.4Gy	43 (45)	11 (61)	32 (63)		25 (58)	18 (69)	
5-fluorouracil-based + 50.4 Gy	26 (38)	7 (39)	19 (37)		18 (42)	8 (31)	
Time interval nCRT to surgery (median, IQR)	8 (7 – 10)	8 (7 – 9)	8 (7 – 10)	0.269	8 (7 – 10)	8 (6 – 9)	0.630

BMI body mass index at diagnosis; *IQR* interquartile range; *NA* not applicable; *pCR* pathologic complete response; *TRG* tumor regression grade; *WHO* World Health Organization
* Clinical T and N status are based on AJCC TNM 7th edition.
Note. P-values in this table were based on χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

different between pCR and non-pCR groups. These findings were consistent with the association between changes in ADC and GR versus non-GR (ΔADC_{during} [median, IQR]: 20% [13%, 33%] for GR versus 8% [0%, 11%] for non-GR, p = 0.008, and ΔADC_{post} [median, IQR]: 24% [13%, 44%] for GR versus 21% [6%, 30%] for non-GR, p = 0.201, Table 2).

Complementary value ^{18}F-FDG PET/CT and DW-MRI parameters

To evaluate the complementary value of ^{18}F-FDG PET/CT and DW-MRI parameters for pCR prediction, receiver operating characteristic (ROC) analyses for ΔADC_{during} combined with $\Delta SUV_{mean,post}$ and histology showed a superior bootstrapped c-statistic in comparison with their individual values and histology (0.83 [95% CI: 0.74 – 0.94] for ΔADC_{during} and $\Delta SUV_{mean,post}$, versus 0.81 [95% CI: 0.70 – 0.93] for ΔADC_{during} and 0.79 [95% CI: 0.67 – 0.90] for $\Delta SUV_{mean,post}$, all models with histology, Table 3 and Figure 3a). Furthermore, the model with ΔADC_{during} $\Delta SUV_{mean,post}$ and histology also demonstrated the best global model fit in terms of the lowest AIC (Supplementary Table 2). ROC curve analyses of ^{18}F-FDG PET/CT and DW-MRI parameters acquired during treatment for prediction of GR did not demonstrate complementary value of ΔADC_{during} and $\Delta SUV_{max,during,}$ but demonstrated a
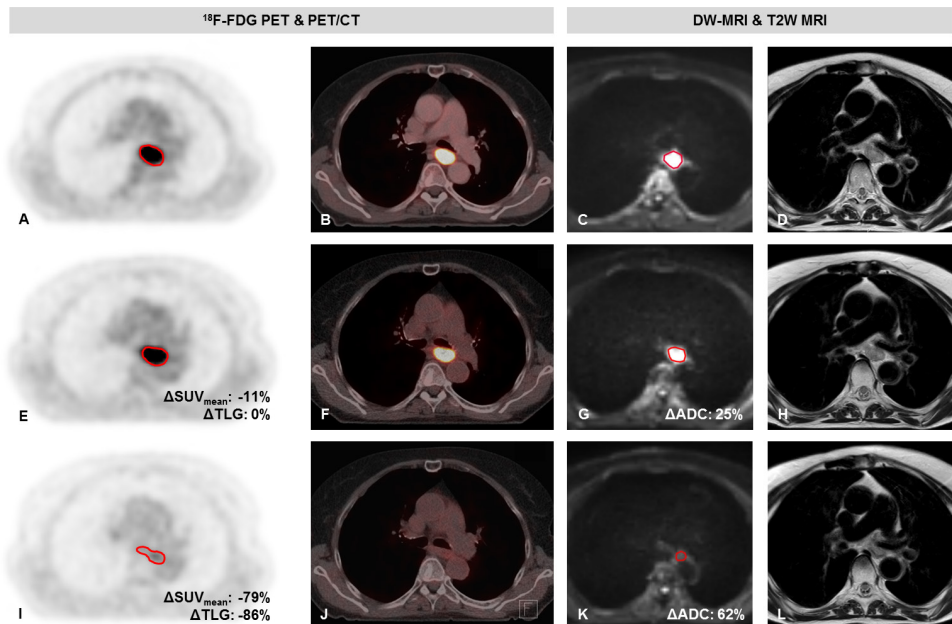
Figure 2. Patient with a cT3N2M0 mid-esophageal squamous cell carcinoma with a pathologic complete response to neoadjuvant chemoradiotherapy (TRG 1). ^{18}F-FDG PET images (**A**, **E**, **I**), fused PET/CT images (**B**, **F**, **J**), diffusion-weighted images (b-value = 200 s/mm^2) (C, G, K) and T2 weighted images (**D**, **H**, **L**) on a 1.5T MR scanner before neoadjuvant chemoradiotherapy (nCRT) (A-D), during nCRT (**E-H**), and after nCRT (**I-L**).

high bootstrapped c-statistic for ΔADC_{during} with histology (0.82 [95% CI: 0.75 – 0.94] for ΔADC_{during} and $\Delta SUV_{max,during}$, versus 0.83 [95% CI: 0.73 – 0.92] for ΔADC_{during} and 0.74 [95% CI: 0.60 – 0.88] for $\Delta SUV_{max,during}$, all models with histology, Table 3 and Figure 3b). The model with $\Delta SUV_{max,during}$ and histology demonstrated the best global model fit in terms lowest AIC (Supplementary Table 2).

Model calibration plots of all 8 models as described in Table 3 are depicted in Supplementary Figure 2, and show variable calibration upon visual inspection. In general, the best model for pCR in terms of highest c-statistic and lowest AIC (the model with DW-MRI, PET-CT and histology, i.e. model 4 in Table 3) was slightly overoptimistic and tended to underestimate the observed probability of pCR, whereas the best model for GR in terms of highest c-statistic (the model with DW-MRI and histology, i.e. model 2 in Table 3) was better calibrated.

Table 2. Relative changes in ^{18}F-FDG PET/CT and DW-MRI parameters between pathologic complete response (TRG 1) and non-pathologic complete response (TRG 2-4), as well as between good response (TRG 1-2) and poor response (TRG 3-4).

| | | Median (IQR) | | Benjamini-Hochberg | |
		pCR (TRG 1) (n=18)	non-pCR (TRG 2-4) (n=51)	p-value*	adjusted p-value	c-statistic
During treatment	ΔSUV_{mean} (%)	-27 (-38, -6)	-19 (-33, -3)	0.246	0.264	0.59
	ΔSUV_{max} (%)	-29 (-46, -8)	-23 (-35, -2)	0.408	0.408	0.57
	ΔTLG_{during} (%)	-54 (-64, -23)	-20 (-50, 10)	0.020	0.052	0.69
	ΔADC_{during} (%)	28 (15, 39)	11 (4, 17)	0.001	0.008	0.77
Post treatment	ΔSUV_{mean} (%)	-63 (-68, -49)	-42 (-58, -16)	0.003	0.016	0.74
	ΔSUV_{max} (%)	-68 (-78, -58)	-54 (-71, -31)	0.026	0.052	0.68
	ΔTLG_{post} (%)	-86 (-93, -81)	-65 (-88, -32)	0.006	0.024	0.72
	ΔADC_{post} (%)	34 (13, 46)	20 (10, 38)	0.139	0.201	0.63

| | | Median (IQR) | | Benjamini-Hochberg | |
		GR (TRG 1-2) (n=43)	non-GR (TRG 3-4) (n=26)	p-value*	adjusted p-value	c-statistic
During treatment	ΔSUV_{mean} (%)	-26 (-42, -5)	-19 (-27, -2)	0.054	0.086	0.64
	ΔSUV_{max} (%)	-31 (-44, -14)	-12 (-29, 2)	0.016	0.051	0.67
	ΔTLG_{during} (%)	-37 (-62, -9)	-17 (-38, 20)	0.024	0.052	0.66
	ΔADC_{during} (%)	20 (13, 33)	7.3 (0, 11)	<0.001	0.008	0.84
Post treatment	ΔSUV_{mean} (%)	-51 (-66, -34)	-42 (-56, -11)	0.042	0.075	0.65
	ΔSUV_{max} (%)	-63 (-76, -44)	-53 (-74, -26)	0.187	0.230	0.60
	ΔTLG_{post} (%)	-81 (-89, -54)	-64 (-88, -35)	0.248	0.264	0.59
	ΔADC_{post} (%)	24 (13, 44)	21 (6, 30)	0.151	0.201	0.61

ADC apparent diffusion coefficient; *c-statistic* concordance statistic; *GR* good response; *IQR* interquartile range; *pCR* pathologic complete response; *SD* standard deviation; *SUV* standardized uptake value; *TLG* tumor lesion glycolysis; *TRG* tumor regression grade
* p-value calculated based on Mann-Whitney U test
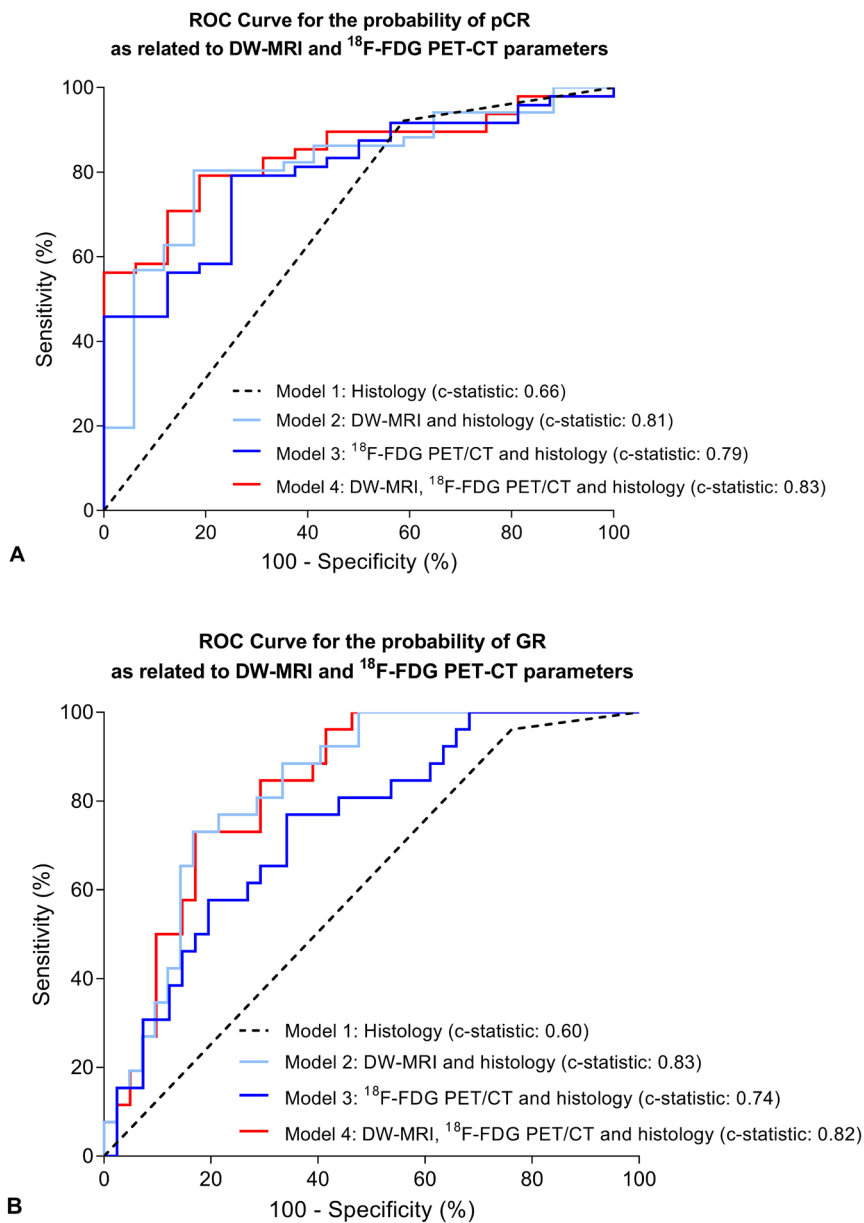
Figure 3. Receiver-operating-characteristic curve analysis for the regression models with DW-MRI and ^{18}F-FDG PET/CT parameters, as well as histopathological tumor type, for discriminating between pathologic complete response (TRG 1) and non-pathologic complete response (TRG 2-4) patients (**A**) as well as between good responders (TRG 1-2, GR) and poor responders (TRG 3-4, non-GR) (**B**).

Table 3. Ridge regression analyses demonstrating the complementary value of 18F-FDG PET/CT and DW-MRI parameters with pathologic complete response (TRG 1) and good response (TRG 1-2) as outcome variables.

	pCR (TRG 1)			GR (TRG 1 + 2)	
Predictors	**Odds ratio**	**Optimism-corrected c-statistic (95% bootstrapped CI)**	**Predictors**	**Odds ratio**	**Optimism corrected c-statistic (95% bootstrapped CI)**
Model 1: Histology					
Squamous cell carcinoma¥	8.23	0.66 (0.53 – 0.78)*	Squamous cell carcinoma¥	7.81	0.60 (0.52 – 0.67)*
Model 2: DW-MRI parameter and histology					
ΔADC_{during} (%)	1.04	0.81 (0.70 – 0.93)*	ΔADC_{during} (%)	1.08	0.83 (0.73 – 0.92)*
Squamous cell carcinoma¥	4.56		Squamous cell carcinoma¥	2.95	
Model 3: 18F-FDG PET/CT parameter and histology					
$\Delta SUV_{mean,post}$ (%)	0.98	0.79 (0.67 – 0.90)§	$\Delta SUV_{max,during}$ (%)	0.99	0.74 (0.60 – 0.88)'
Squamous cell carcinoma¥	3.90		Squamous cell carcinoma¥	3.12	
Model 4: DW-MRI and 18F-FDG PET/CT parameters and histology					
ΔADC_{during} (%)	1.03	0.83 (0.74 – 0.94)§	ΔADC_{during} (%)	1.06	0.82 (0.75 – 0.94)'
$\Delta SUV_{mean,post}$ (%)	0.98		$\Delta SUV_{max,during}$ (%)	0.99	
Squamous cell carcinoma¥	3.19		Squamous cell carcinoma¥	3.14	

ADC apparent diffusion coefficient; *CI* confidence interval; *c-statistic* concordance statistic; *GR* good response (TRG 1-2); *pCR* pathologic complete response; *SUV* standardized uptake value.

* Analyses based on 68 patients of whom 17 had pCR (TRG 1) and 42 had GR (TRG 1-2). The applied exclusion criterion was histology other than adenocarcinoma or squamous cell carcinoma (n=1).

§ Analyses based on 64 patients of whom 16 had pCR (TRG 1). Exclusion criteria were no post-treatment 18F-FDG PET/CT available (n=3), no uptake on post-treatment 18F-FDG PET/CT (n=1) and histology other than adenocarcinoma or squamous cell carcinoma (n=1).

' Analyses based on 67 patients of whom 41 had GR (TRG 1-2). Exclusion criteria were no 18F-FDG PET/CT available during treatment (n=1) and histology other than adenocarcinoma or squamous cell carcinoma (n=1).

¥ Adenocarcinoma was used as reference category.

Note. For the analyses of good response only 18F-FDG PET/CT and DW-MRI parameters acquired during neoadjuvant chemoradiotherapy were included in the analyses considering the relevance of the research question. Regression coefficients and intercepts of all models are included in the supplementary file.

Table 4. Multivariable Cox regression analyses for overall survival (OS) and disease free survival (DFS) based on the model with DW-MRI and ^{18}F-FDG PET/CT parameters and histology.

	Predictors	Hazard ratio (95% CI)
Overall survival*	ΔADC_{during} (%)	0.98 (0.95 – 1.01)
	$\Delta SUV_{mean,post}$ (%)	0.99 (0.97 – 1.01)
	Squamous cell carcinoma[¥]	0.67 (0.21 – 2.16)
Disease free survival§	ΔADC_{during} (%)	0.98 (0.95 – 1.01)
	$\Delta SUV_{mean,post}$ (%)	1.00 (0.98 – 1.01)
	Squamous cell carcinoma[¥]	0.65 (0.17 – 2.44)

ADC apparent diffusion coefficient; *CI* confidence interval; *SUV* standardized uptake value; *TLG* tumor lesion glycolysis; *TRG* tumor regression grade

* Analyses based on 63 patients of whom 27 deceased during follow-up. The applied exclusion criteria were no post-treatment ^{18}F-FDG PET/CT available (n=3), no uptake on post-treatment ^{18}F-FDG PET/CT (n=1), histology other than adenocarcinoma or squamous cell carcinoma (n=1) and incomplete follow-up data (n=1).

§ Analyses based on 57 patients of whom 24 had disease recurrence during follow-up. The applied exclusion criteria were no post-treatment ^{18}F-FDG PET/CT available (n=3), no uptake on post-treatment ^{18}F-FDG PET/CT (n=1), histology other than adenocarcinoma or squamous cell carcinoma (n=1), incomplete follow-up data (n=5) and censored before earliest event (n=1).

[¥] Adenocarcinoma was used as reference category.

Survival

The results of the multivariable Cox regression analysis for OS and DFS including the parameters from the most accurate model for pCR prediction are depicted in Table 4. None of the included imaging parameters (ΔADC_{during} and $\Delta SUV_{mean,post}$), nor histology was significantly associated with OS or DFS, as all 95% CI of the hazard ratio's crossed the null hypothesis.

Discussion

This international multicenter, prospective study was designed to assess the predictive value of quantitative changes on ^{18}F-FDG PET/CT and DW-MRI scans acquired during and after nCRT in patients with esophageal cancer. Changes in ^{18}F-FDG PET/CT parameters *after* nCRT ($\Delta SUV_{mean,post}$ and ΔTLG_{post}), as well as changes in DW-MRI parameters *during* nCRT (ΔADC_{during}) demonstrate to discriminate well between pathologic complete responders (TRG 1) and non-pCR (TRG 2-4) in esophageal cancer. Moreover, ^{18}F-FDG PET/CT and DW-MRI might be of complementary value in the assessment of histopathological response. However, the prediction model including both imaging features did not correspond with OS or DFS in a subsequent experimental analysis on long-term clinical outcomes.

This study provides encouraging results for the potential value of multimodal imaging in discrimination of patients likely to have pCR to nCRT. This is of important clinical value, as accurate response prediction would enable physicians to individualize and adapt therapy

for each individual patient. Considering the postoperative morbidity and mortality associated with surgery, and the effect of surgery on quality of life, an organ-sparing approach might improve outcomes for patients with pCR.[31-33] Whereas in patients with a poor response to nCRT, alternative treatment strategies could be explored such as intensification or additional neoadjuvant treatment, or ineffective therapy could be stopped. For this latter purpose, a model was developed based on changes in ^{18}F-FDG PET/CT and DW-MRI parameters *during* nCRT, with GR (TRG 1-2) as outcome variable, demonstrating a high predictive performance of a DW-MRI parameter and tumor histology (c-statistic 0.83).

Until now, most imaging studies in esophageal response prediction have focused on a single modality. Two meta-analyses on the value of ^{18}F-FDG PET/CT suggested that the decrease in mean or maximum metabolic activity within the first two weeks of nCRT are so far the best available predictor of treatment response.[14,19] However, the conclusion of these meta-analyses, including a more recent extensive analysis, is that the discriminatory ability of ^{18}F-FDG PET/CT was insufficient for clinical decision-making.[20] The results of this study are consistent with these findings, with a maximum c-statistic of 0.74 for an ^{18}F-FDG PET/CT imaging parameter (ΔSUV_{mean} after nCRT). Our study results are also consistent with the findings of more recent studies that showed no significant associations between relative changes ^{18}F-FDG PET/CT imaging parameters for pCR, or only for ΔTLG_{during}.[17,27]

A pilot study using DW-MRI reported that the change in the tumor ADC during the first 2-3 weeks of nCRT for esophageal cancer seemed highly predictive for pCR.[16] These findings have recently been externally validated in another single-center pilot study[17], but have not yet been validated in a larger cohort. The current, larger and multicenter study confirms these findings, reporting the highest c-statistic for prediction of pCR and GR for ΔADC_{during} (0.77 and 0.84, respectively). Addition of ^{18}F-FDG PET/CT parameters to the DW-MRI model raised the ability to discriminate between pCR (TRG 1) and non-pCR (TRG 2-4) in 83% of the patients (c-statistic: 0.83).

As an illustration, the patient with an squamous cell carcinoma – whose scans are depicted in Figure 2 – and a ΔADC_{during} of 25% and $\Delta SUV_{mean,post}$ of -79%, has a predicted probability of 0.69 for a pCR as based on the model including ^{18}F-FDG PET/CT, DW-MRI parameters and histology. A patient with an adenocarcinoma and ΔADC_{during} of 10% and $\Delta SUV_{mean,post}$ of -20%, would have only had a predicted probability 0.12 for pCR based on the model. It is unclear yet what predictive power is required for clinical decision making as this might vary between patients. It could well be argued that for high risk surgical patients with significant comorbidities, a lower accuracy of a predicted pCR might be deemed sufficient to postpone standard esophagectomy, whereas for younger, low risk surgical patients, a higher accuracy might be desired. Other considerations to be taken into account are how many patients will require salvage surgery, and how many patients will have missed an

opportunity for cure because surgery was initially avoided, as death of locoregional disease will be considered as the ultimate failure of therapy. Eventually, future improvement in prognostication will likely result in stratification of patients by risk of surgery balanced with the predicted probability of pCR.

Other strategies to identify good responders are currently subject of research in multiple trials. The recently published preSANO study focused on accurate detection of locoregional residual disease rather than pathologic complete response, and reported favorable results for response evaluations using EUS, bite-on-bite biopsies, fine-needle aspiration of suspicious lymph nodes and ^{18}F-FDG PET/CT.[34] Furthermore, it has been recently recognized that the combination of clinical and imaging parameters with molecular biomarkers might be the key to success. Besides molecular markers — such as ALDH1 and GLI1/HH — which might predict response before nCRT, other molecular markers, such as circulating tumor DNA (ctDNA), that evaluate response after completion of nCRT should be further explored.[35,36] A large Dutch multicenter study is currently investigating the additional value of ctDNA to ^{18}F-FDG PET/CT and MRI for accurate pCR prediction (PRIDE study).[37]

Since ^{18}F-FDG PET/CT and DW-MRI scanning during and after completion of nCRT are currently not part of standard imaging evaluation, the predictive value of multimodal imaging evaluation should be considered in light of the associated costs and physical burden to the patients of repeated imaging procedures. Previous studies have demonstrated that ^{18}F-FDG PET/CT and MRI are generally well-tolerated imaging procedures for the assessment of response to treatment in esophageal cancer patients.[38] Furthermore, long-term treatment outcomes (survival and long-term quality of life) appear to outweigh short-term attributes (short-term quality of life and burden of surveillance examinations with endoscopy and PET/CT) in another study.[39] In this perspective, further investigation of multimodal strategies for reliable response prediction to nCRT seems justified.

Several challenges exist before routine ^{18}F-FDG PET/CT and DW-MRI scanning for treatment response assessment can be implemented for clinical practice. First, quantitative imaging values such as SUV_{max} from ^{18}F-FDG PET/CT imaging are influenced by vendor specific characteristics, which differ between the scanner platforms. However, since our study only included relative changes in the analyses, the impact of these differences on the results is limited. Standardization of the DW-MRI protocols is more challenging than for ^{18}F-FDG PET/CT protocols, as they are comprised of more nuanced sequences that are more likely to differ between institutions.[40,41] The MRI scan protocol applied in the current study was clinically developed specifically for esophageal cancer patients, and extensive efforts have been undertaken to synchronize the protocols before initiation of the study. Even though standardization of MRI protocols appears to be challenging, previous studies have found similar changes in mean tumor ADC during nCRT in esophageal cancer to be

predictive of pCR, despite major differences in scanner platforms (3.0T versus 1.5T, GE versus Philips).[16,17] Furthermore, our study included both scanner types and found consistent results with the earlier studies.

Second, it became apparent during the assessment of the DW-MRI scans in our study that there is still room for improvement in the quality of these scans. The thorax is a challenging region for MR imaging, given the differences in magnetic susceptibility between the organs of the thorax (e.g., pulmonary parenchyma, vertebrae and ribs), as well as the effects of cardiac and respiratory motion.[42] As such, MR imaging in the thoracic region remains under continuous technical development, and better imaging quality may have the potential to further improve the performance of DW-MRI for treatment response assessment.[43]

Third, even though semi-automatic contouring methods were used, differences between contouring techniques and inter-reader variability could still be an issue. However, the reproducibility of ADC measurements between readers has been studied previously, and was considered reproducible among 5 readers in a relatively small dataset of 20 esophageal cancer patients.[17] These high correlations were achieved when ADC values were assessed with whole volume tumor ADC measurements, as in our study. As semi-automatic tumor delineation on ^{18}F-FDG PET/CT and DW-MRI scans remains a time-consuming process, the clinical applicability of ^{18}F-FDG PET/CT and DW-MRI for response assessment might benefit from a validated fully automatic contouring tool.

Fourth, the prediction model including both imaging features that provided good performance for prediction of pCR did not correspond with OS or DFS in a subsequent experimental analysis. We believe that the survival analyses in the current study should be interpreted with caution, as these survival analyses were not predefined and hence may suffer from a lack of power. Also, it is essential to first develop a clinically useful prediction model to identify complete responders, before drawing any conclusions regarding survival. Especially since subsequent analyses with survival will only make sense if identification of pCR is accurate and treatment is altered based on these predictions, as the burden of 3 additional MRI's and 1 additional PET/CT (as in the current study) can only be justified if this results in treatment alterations, and not just for prognostic purposes.

Lastly, limitations of the current study include the absence of an external validation cohort to validate our results and the various nCRT regimens applied. However, consistent findings in a slightly heterogeneous, multicenter study population confers external validity to the results of the study (Supplementary Table 1). Other strengths of the current study include the availability of histopathological evaluation as a reference standard, instead of surrogate endpoints such as radiological response criteria (RECIST), and the inclusion of histologic subtypes in the multivariable analyses.

In conclusion, our study shows that quantitative ADC changes from baseline to interim DW-MRI scans and SUV_{mean} changes from baseline to follow-up ^{18}F-FDG PET/CT scans

can help identify pCR to nCRT in esophageal cancer patients. However, additional larger prospective studies, as well as other combined multimodal approaches are needed to validate these results, especially regarding the potentially complementary value of ^{18}F-FDG PET/CT and DW-MRI imaging parameters.

5

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5

SUPPLEMENTARY MATERIAL

Methods

Exclusion criteria

Exclusion criteria included an age of <18 years, previous treatment with thoracic surgery or thoracic radiotherapy, and contraindications for ^{18}F-FDG PET/CT or MRI. The diagnostic work-up consisted of an endoscopy with biopsy for diagnosis, as well as EUS and integrated ^{18}F-FDG PET/CT. In addition, patients who were initially included in the study but eventually did not undergo surgery were excluded from further analyses.

Survival

Survival data was completed for all but 1 patient (n=68) at least up to 18 months after date of surgery (median [IQR] time to censoring: 37 months [33 – 49 months]). Data on disease recurrence and disease free survival (DFS) was completed for all but 5 patients (n=63). Disease recurrence was defined as local or distant recurrence, either based on imaging or histopathological assessment.

^{18}F-FDG PET/CT scan parameters

The timing of the ^{18}F-FDG PET/CT scan in the second or third week of treatment was based on previous studies which demonstrated a potentially superior accuracy at this time point as compared to pre-treatment and post-treatment scanning only.[1,2] The ^{18}F-FDG PET examinations were performed on dedicated PET/CT systems. Patients were instructed to fast for at least 6 hours before ^{18}F-FDG PET and a glucose level within the normal range (80-120 mg/dl) was confirmed. Before ^{18}F-FDG PET, a CT scan without contrast agent was acquired for attenuation correction purposes. ^{18}F-FDG PET scans were acquired 60-90 minutes after administration of ^{18}F-FDG with a dose ranging between 190-370 MBq, in three-dimensional (3D) acquisition mode at 2-5 minutes per bed position.

DW-MRI scan parameters

The DW-MRI examinations were either performed on a 1.5T (UMC Utrecht and NKI-AVL; Achieva, Philips Medical Systems, Best, The Netherlands) or on a 3.0T scanner (MDACC; Discovery MR750, GE Healthcare, Milwaukee, Wisconsin, USA). Transverse diffusion-weighted images were obtained with free breathing and using 3 different b-values (b = 0, 200 and 800 s/mm^2).

Image analysis – tumor delineations

^{18}F-FDG PET/CT imaging analysis, including primary tumor delineation and calculation of metabolic and volumetric parameters, was performed using commercially available software (MIM Software, Cleveland, Ohio, USA). The primary tumor volume was defined as the volume of interest (VOI) and contoured using a semi-automatic gradient-based delineation method – which has been validated in a multi-observer study reporting superior accuracy, consistency and robustness compared with manual and threshold methods[3] – followed by manual editing by two readers.

DW-MRI analysis was performed using an imaging analysis software package (ImageI).[4] The primary tumor – excluding the lumen – was delineated on the DW-MRI scans with a b-value of 200 s/mm^2 using semi-automatic contouring, allowing for manual editing by one reader.[4] Contouring of the tumor was performed conservatively to avoid the edges of the tumor boundaries, as ADC values in the periphery of the tumor may be unreliable due to motion or other image distortions. The DW-MRI scans with b-values of 0, 200, and 800 s/mm^2 were fitted with a mono-exponential model to generate quantitative ADC maps for each slice.[5–7]

Statistical analysis

Clinical characteristics that potentially predict response were pre-specified based on previous literature (i.e., clinical T status, histologic subtype, neoadjuvant chemoradiotherapy regimen and time interval from nCRT to surgery) and were compared between patients with pCR (TRG 1) and non-pCR patients (TRG 2-4), and between good responders (TRG 1-2, GR) and poor responders (TRG 3-4, non-GR) based on the χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

The relative changes of the ^{18}F-FDG PET/CT and DW-MRI parameters were also compared between these patient groups using the Mann-Whitney U test to validate findings of previous pilot-studies.[5,7–12] Benjamini-Hochberg corrections were applied to adjust for multiple comparisons and therewith minimizing the false discovery rate.[13] The ability of single modality ^{18}F-FDG PET/CT and DW-MRI parameters to discriminate between different pathologic response groups was quantified using the area under the receiver operating characteristic (ROC) curve (c-statistic).

Secondly, the complementary value of ^{18}F-FDG PET/CT and DW-MRI parameters was assessed using multivariable penalized Ridge regression models to reduce model overfitting in a situation with few events per variable.[14] The applied overall penalty (λ_{min}) represents the minimum mean cross-validated error, which was obtained using 10-fold cross validation. Optimism-corrected c-statistics of the Ridge regression models were obtained by bootstrap resampling.[15] The original dataset was a 1,000 times resampled with replacement to obtain a dataset of the same size. All models were then fitted to the 1,000

bootstrap samples. Each fitted model was then applied both to the resampled dataset from which it was generated, and to the original dataset. The optimism corrected c-statistic was calculated as the original c-statistic minus the optimism, which was calculated as the difference between the c-statistic on the original dataset and the resampled dataset. Also, bootstrapping allowed for reconstruction of 95% confidence intervals (CI) around the c-statistic. The global fit of the models was compared using Akaike Information Criterion (AIC), with the lowest AIC representing the best fit.[16,17] Model calibration of the models was evaluated by visual inspection of the model calibration plots.[17] Variables to be entered in the penalized regression models with pCR or GR as outcome were histopathological tumor type – which an important factor to impact pathologic response to nCRT based on previous literature – and the ^{18}F-FDG PET/CT and DW-MRI parameter with the highest c-statistic in univariable analyses.

Separate analyses were performed on pCR (TRG 1) versus non-pCR (TRG 2-4), and GR (TRG 1-2) versus non-GR (TRG 3-4). The first analysis aimed at aiding clinical decision-making regarding omission of surgery in anticipated complete responders, whereas the second analysis was deemed as more relevant for potentially modifying or discontinuing nCRT early during treatment. For the latter purpose, only ^{18}F-FDG PET/CT and DW-MRI parameters *during* nCRT were taken into account, as knowledge of response after completion of nCRT would be irrelevant for modification of nCRT.

In order to evaluate whether the best performing model for pCR prediction based on the aforementioned analyses correlate with overall survival (OS) and disease free survival (DFS), multivariable Cox regression analyses were performed with estimation of hazard ratio's (HR) and 95% CI for the included predictors.

All statistical analyses were performed using R 3.1.2 open-source software ('pROC', 'glmnet', 'boot' and 'rms' packages, http://www.R-project.org). A p-value of <0.05 was considered statistically significant.

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5

Supplementary Table 1. Tumor regression grades (TRG) per histologic subtype and per treatment regimen.

Treatment regimen	Histologic subtypes	TRG 1	TRG 2	TRG 3	TRG 4	Total
Full cohort	Adenocarcinoma	10 (17.5%)	22 (38.6%)	19 (33.3%)	6 (10.5%)	57 (100%)
	Squamous cell carcinoma	7 (63.6%)	3 (27.3%)	1 (9.1%)	0 (0%)	11 (100%)
	Undifferentiated large cell carcinoma	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Carboplatin/ paclitaxel + 41.4 Gy (UMC Utrecht, NKI-AVL)	Adenocarcinoma	4 (11.8%)	12 (35.3%)	12 (35.3%)	6 (17.6%)	34 (100%)
	Squamous cell carcinoma	6 (75%)	2 (25%)	0 (0%)	0 (0 %)	8 (100%)
	Undifferentiated arge cell carcinoma	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
5-fluorouracil-based + 50.4 Gy (MDACC)	Adenocarcinoma	6 (26.1%)	10 (43.5%)	7 (30.4%)	0 (0%)	23 (100%)
	Squamous cell carcinoma	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)	3 (100%)

Data are numbers of patients, with row-based percentages in parentheses.
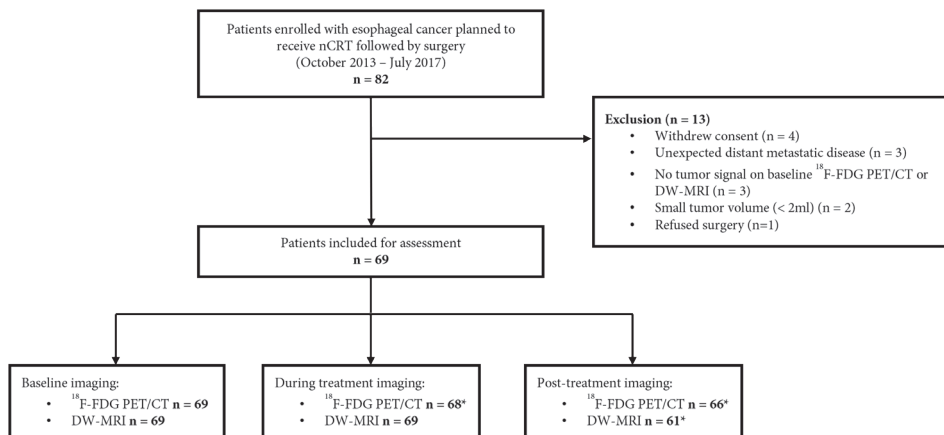
* Not available due to patients' refusal or an unexpectedly antedated surgical resection.

Supplementary Figure 1. Study profile.
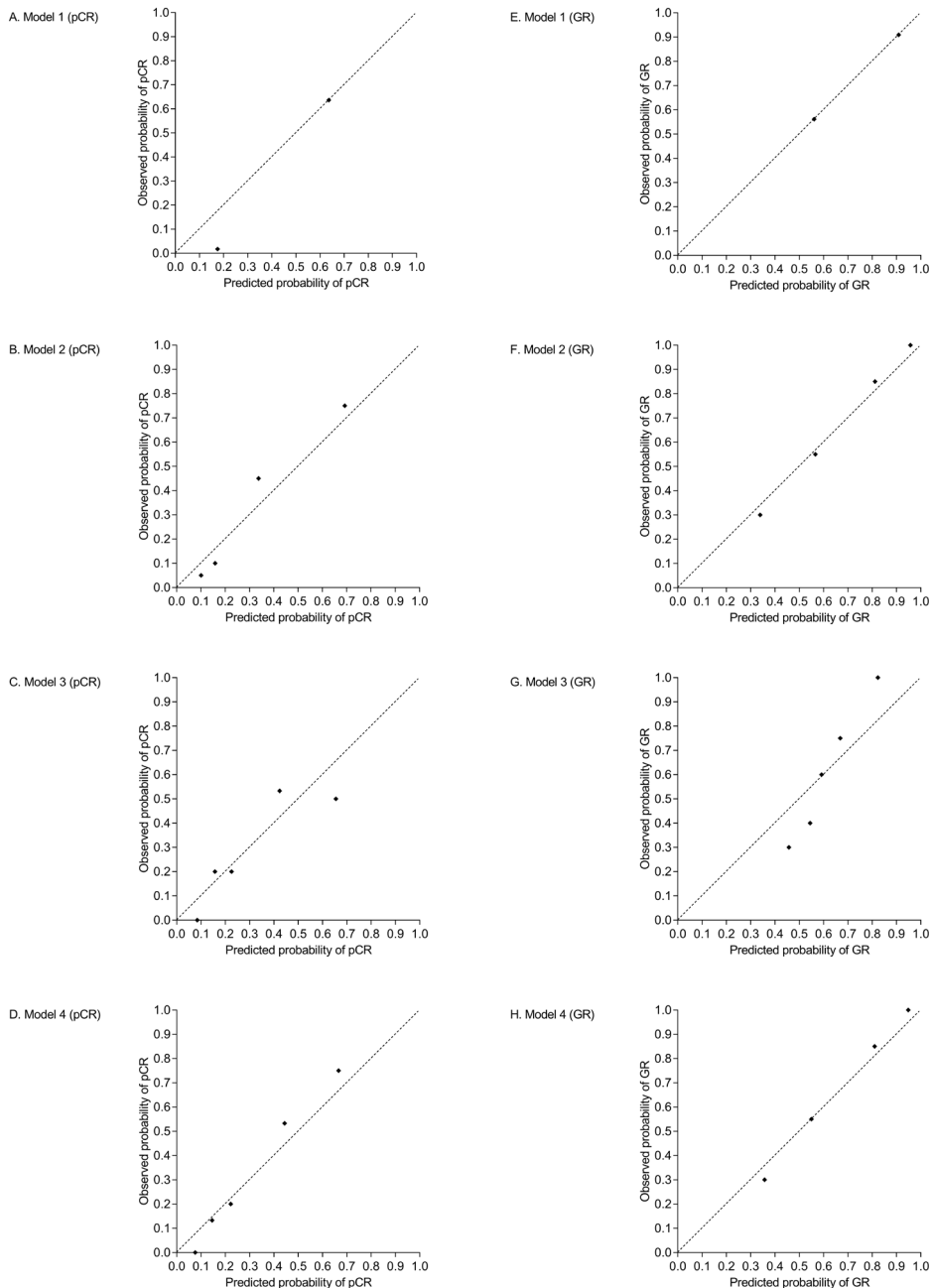
Supplementary Figure 2. Calibration plots of the penalized regression models as described in Table 3 for pathologic complete response (pCR) prediction (**A-D**) and good response (GR) prediction (**E-H**).

Supplementary Table 2. Intercepts and regression coefficients for Ridge regression analyses on the complementary value of ^{18}F-FDG PET/CT and DW-MRI parameters with pathologic complete response (TRG 1) and good response (TRG 1-2) as outcome variables.

pCR (TRG 1)			GR (TRG 1 + 2)		
Intercept and predictors	**β**	**AIC**	**Intercept and predictors**	**β**	**AIC**
Model 1: Histology					
Intercept	-1.55	71.36	Intercept	0.25	88.85
Squamous cell carcinoma¥	2.10		Squamous cell carcinoma¥	2.06	
Model 2: DW-MRI parameter and histology					
Intercept	-2.20	64.73	Intercept	-0.71	85.83
ΔADC_{during} (%)	0.04		ΔADC_{during} (%)	0.08	
Squamous cell carcinoma¥	1.52		Squamous cell carcinoma¥	1.08	
Model 3: ^{18}F-FDG PET/CT parameter and histology					
Intercept	-2.51	61.32	Intercept	0.12	71.64
$\Delta SUV_{mean,post}$ (%)	-0.02		$\Delta SUV_{max,during}$ (%)	-0.01	
Squamous cell carcinoma¥	1.36		Squamous cell carcinoma¥	1.14	
Model 4: DW-MRI and ^{18}F-FDG PET/CT parameters and histology					
Intercept	-2.68	61.13	Intercept	-0.69	72.31
ΔADC_{during} (%)	0.03		ΔADC_{during} (%)	0.06	
$\Delta SUV_{mean,post}$ (%)	-0.02		$\Delta SUV_{max,during}$ (%)	-0.01	
Squamous cell carcinoma¥	1.16		Squamous cell carcinoma¥	1.14	

ADC apparent diffusion coefficient; *AIC* Akaike Information Criterion; *GR* good response (TRG 1-2); *pCR* pathologic complete response; *SUV* standardized uptake value
¥ Adenocarcinoma was used as reference category.

Optimal timing for prediction of pathologic complete response to neoadjuvant chemoradiotherapy with diffusion-weighted MRI in patients with esophageal cancer

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Abstract

Objective
To determine the optimal timing of diffusion-weighted magnetic resonance imaging (DW-MRI) for prediction of pathologic complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer.

Methods
Patients with esophageal adenocarcinoma or squamous cell carcinoma planned to undergo nCRT followed by surgery were enrolled in this prospective study. Patients underwent 6 DW-MRI scans: 1 baseline scan before start of nCRT and weekly scans during 5 weeks of nCRT. Relative changes in mean apparent diffusion coefficient (ADC) values between the baseline scans and the scans during nCRT (ΔADC(%)) were compared between pathologic complete responders (pCR) and non-pCR (tumor regression grades 2-5). The discriminative ability of ΔADC(%) was determined based on the c-statistic.

Results
A total of 24 patients with 142 DW-MRI scans was included. pCR was observed in 7 patients (29%). ΔADC(%) from baseline to week 2 was significantly higher in patients with pCR versus non-pCR (median [IQR]: 36% [30%, 41%] for pCR versus 16% [14%, 29%] for non-pCR, p = 0.004). The ΔADC(%) of the second week in combination with histology resulted in the highest c-statistic for the prediction of pCR versus non-pCR (0.87). The c-statistic of this model increased to 0.97 after additional exclusion of patients with a small tumor volume (<7 mL, n=3) and tumor histology of the resection specimen other than adenocarcinoma or squamous cell carcinoma (n=1).

Conclusion
The relative change in tumor ADC (ΔADC(%)) during the first 2 weeks of nCRT is the most predictive for pathologic complete response to nCRT in esophageal cancer patients.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is considered the standard of care for locally advanced, resectable esophageal cancer without distant metastases.[1,2] Through tumor downsizing and downstaging, nCRT improves locoregional control and overall survival rates compared to surgery alone.[2-4] The degree of tumor regression in response to nCRT is directly related to long-term survival, with pathologic complete response (pCR) resulting in the most favorable long-term prognosis.[4,5] A pCR, defined as the absence of viable tumor cells at the site of the primary tumor after nCRT, is observed in around 16-29% of the patients after nCRT.[2,6,7] For these pathologic complete responders, it is questioned whether they benefit from a subsequent esophagectomy, which is associated with substantial morbidity and impaired quality of life.[8-13] In order to study the safety and feasibility of postponing or even omitting esophagectomy in these patients, accurate prediction of complete responders is essential.

Diffusion weighted magnetic resonance imaging (DW-MRI) is one of the modalities that is actively studied for its potential in treatment response assessment in multiple cancers, including esophageal cancer.[14-20] DW-MRI is an appealing imaging technique because it is a quantitative method, noninvasive, relatively fast and without exposure to ionizing radiation.[21] It depends on the microscopic mobility of water and is highly influenced by tissue cellularity and tissue organization.[21] Treatment with chemoradiotherapy can result in the loss of cell membrane integrity and apoptosis and this process can be detected as an increase in the mean tumor apparent diffusion coefficient (ADC).[22] However, a subsequent decrease in tumor ADC values may occur by fibrosis, which may complicate interpretation and predictive ability for treatment response.[23] Previous studies have shown promising results for DW-MRI before nCRT, as well as during the first 2-3 weeks of nCRT in the prediction of pathologic response in esophageal cancer patients.[14,15,24-27] To investigate and further optimize the predictive ability of DW-MRI during nCRT for response assessment in esophageal cancer, this study aimed at establishing the optimal timing of DW-MRI scanning during nCRT for the prediction of pCR in patients with esophageal squamous cell carcinoma and adenocarcinoma.

Methods

This single center, prospective cohort study was approved by the institutional review board of the University Medical Center Utrecht (protocol ID 15-340). All participants provided written informed consent. The primary aim of the study was to research intra-fraction tumor motion and regression in order to develop patient-specific adaptive radiotherapy

using MRI.[28,29] The current analysis on the optimal timing for response prediction was a prespecified secondary aim of this prospective study, hence, not all patients who were eligible for inclusion in the prospective study were analyzed in the current analysis.

Study population

Consecutive patients with histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction who were scheduled to undergo nCRT followed by esophagectomy between December 2015 and April 2018 were eligible for inclusion in the current analysis. Exclusion criteria for enrollment in the study included age <18 years, previous treatment with thoracic surgery or thoracic radiotherapy, and contraindications for MRI. Exclusion criteria for the current analysis included unexpected distant metastatic disease after nCRT, poor tumor visibility on DW-MRI or withdrawal from study participation. The primary diagnostic work-up consisted of an endoscopy with biopsy for diagnosis, as well as an integrated ^{18}F-FDG PET/CT scan for clinical staging.

Treatment

The neoadjuvant treatment regimen consisted of weekly intravenous administration of carboplatin and paclitaxel for 5 weeks with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy, see Supplementary Material for details).[2] Surgical resection consisted of a transthoracic or transhiatal esophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction with either cervical or intrathoracic anastomosis.

Histopathological assessment

The surgical resection specimen was assessed by a specialized gastrointestinal pathologist who was blinded for the results of the DW-MRI scans. Patients were staged in accordance with the 7th edition of the Union for International Cancer Control (UICC).[30] Pathologic tumor regression was reported according to the Mandard system (tumor regression grade [TRG] 1 [pCR, ypT0]: complete response with absence of residual cancer cells, TRG 2: rare residual cancer cells scattered through fibrosis, TRG 3: increase in the number of residual cancer cells, but fibrosis still predominates, TRG 4: residual cancer outgrowing fibrosis, TRG 5: absence of regressive changes).[31] In the absence of macroscopic tumor, any abnormally appearing tissue was evaluated in order to make an adequate assessment of the presence of residual tumor and the effects of therapy.

Image acquisition

Patients underwent 6 sequential MRI scans. One baseline MRI scan was performed at a median of 5 days (interquartile range [IQR]: 4-8 days) prior to nCRT in addition to the

conventional diagnostic work-up. Subsequently, 5 additional MRI scans were performed weekly during nCRT (see Supplementary Figure 1 for the study design).

All images were acquired on a 1.5T Philips Ingenia. Respiratory-triggered transverse anatomical T2-weighted scans (tT2W) and DW-MRI scans with 3 b-values (0, 200 and 800 s/mm^2) were acquired in coronal planes (see Supplementary Methods for details).

Image analysis

The primary tumor – excluding the lumen – was delineated based on the signal of the baseline DW-MRI scans with a b-value of 800 s/mm^2 using open source software with a semi-automated delineation method (ITK-SNAP, www.itksnap.org),[32,33] allowing for manual editing by 2 readers (A.S.B. and S.E.H.) in consensus. The primary contouring was propagated to the DW-MRI scans of the subsequent weeks, followed by manual adjustment by 1 reader (A.S.B.) based on signal reduction on the b800 DW-MRI scans and tumor regression on the tT2W scans using in-house developed delineation software.[34] Contouring was performed conservatively to avoid edges of the tumor boundaries, as ADC values at the boundaries might be unreliable due to motion or image distortions.[15] In all cases, the apparent tumor bed was verified based on the tT2W images. Since the in-house developed delineation software interprets images as 3D volumes, there was no need to generate multiplanar reconstructions. The readers were blinded to patient-related characteristics and clinical outcome in terms of pathologic response.

ADC maps were generated for each slice based on a mono-exponential model fitted on b-values of 0, 200 and 800 s/mm^2, as based on earlier experience.[14,15] Mean tumor ADC values were extracted from the DW-MRI volume of interests. The relative changes in mean ADC values between the baseline scans and the scans during nCRT were calculated and included in the analyses, as based on previous literature (ΔADC(%) = [mean ADC$_{week(n)}$ – mean ADC$_{baseline}$] / mean ADC$_{baseline}$).[14,15,24]

Statistical analysis

Patient and treatment-related characteristics are described as counts with percentages, mean (± standard deviation [SD]) or median (IQR). The median delineated tumor volume on the baseline DW-MRI scan was compared between patients with a pCR and non-pCR using the nonparametric Mann-Whitney U test.

In order to determine the optimal timing of DW-MRI scanning for prediction of pCR, the ΔADC(%) was compared between patients with a pCR and non-pCR per week using the Mann-Whitney U test. The ability of the ΔADC(%) parameters per week to discriminate between pCR and non-pCR was quantified using ridge regression, including tumor histology as determined on the tumor biopsy – an important known factor to impact pCR. Subsequently, the area under the receiver operating characteristic (ROC) curve (c-statistic)

was calculated. Missing ADC values were imputed with multiple imputation. Subsequently, ΔADC(%) values were calculated and the ridge regression model was fitted on all imputed datasets (see Supplementary material for details).

Furthermore, in order to determine whether the results of future studies could be optimized when applying additional exclusion criteria, a post-hoc sensitivity analysis was performed. Patients with small tumor volumes (as the signal blurring caused by respiratory motion is more pronounced in small tumors) as well as patients with a histologic tumor type other than adenocarcinoma or squamous cell carcinoma based on the resection specimen were excluded. The performance measure of interest in this sensitivity analysis was the c-statistic. All statistical analyses were performed using R software for statistical computing version 3.5.1 ('mice'[35], 'glmnet'[36] and 'Hmisc'[37] packages, www.R-project.org). The significance level was set at $p < 0.05$. No corrections for multiple testing were performed, as the universal null hypothesis was not of interest.[38] Furthermore, as this study was of descriptive nature, no formal power calculation was performed.

Results

Patients

A total of 32 patients with newly diagnosed esophageal cancer were enrolled in the prospective study. Of these patients, 8 were excluded for the current analysis based on unexpected distant metastatic disease after nCRT (n = 2), tumor histology other than squamous cell carcinoma or adenocarcinoma as based on the primary tumor biopsy (n = 2), poor tumor visibility on DW-MRI (n = 3) or withdrawal from study participation (n = 1) (Supplementary Figure 2). The final study population comprised 24 patients with a mean age of 65 years (± 8 years) and all but 2 were male (92%). The majority of the patients had an adenocarcinoma (67%). Median time between nCRT and esophagectomy was 10 weeks (IQR: 7-14 weeks). A pCR (TRG 1) after nCRT was observed in 7 patients (29%). Table 1 gives an overview of the clinical characteristics of the study population.

All patients received 5 cycles of chemotherapy and the full course of radiation therapy. In 1 patient it was decided during nCRT to extend the regimen with 1 week, to a total dose of 50.4 Gy and 6 cycles of chemotherapy. Pre-treatment DW-MRI scans were available in all patients. Two DW-MRI scans during nCRT were missing due to patient's refusal (n=1) or image acquisition problems (n=1), resulting in a total of 142 MRI scans.

The median delineated tumor volume on the baseline DW-MRI scan was 15 mL (IQR: 11 – 23 mL) and did not significantly differ between pCR and non-pCR patients (median [IQR]: 11 mL [7 – 22 mL] versus 16 mL [11 – 23 mL], respectively, p = 0.318).

Table 1. Clinical characteristics of the study population.

Characteristic	Full cohort (n = 24) n	(%)	pCR (n = 7) n	(%)	non-pCR (n = 17) n	(%)
Age at diagnosis, in years (mean ± SD)	65 ± 8		68 ± 7		64 ± 8	
Sex						
Male	22	92%	7	100%	15	88%
Female	2	8%	0	0%	2	12%
Tumor location						
Middle esophagus	1	4%	0	0%	1	6%
Distal esophagus	22	92%	7	100%	15	88%
Gastroesophageal junction	1	4%	0	0%	1	6%
Clinical T stage*						
cT2	1	4%	0	0%	1	6%
cT3	23	96%	7	100%	16	94%
Clinical N stage*						
cN0	8	33%	3	43%	5	29%
cN1	13	54%	2	29%	11	65%
cN2	2	8%	2	29%	0	0%
cN3	1	4%	0	0%	1	6%
Histologic tumor type (biopsy)						
Adenocarcinoma	16	67%	3	43%	13	76%
Squamous cell carcinoma	8	33%	4	57%	4	24%
Tumor regression grade (TRG)						
TRG 1 (pCR)	7	29%	7	100%	NA	
TRG 2	6	25%	NA		6	35%
TRG 3	7	29%	NA		7	41%
TRG 4	3	13%	NA		3	18%
TRG 5	1	4%	NA		1	6%
Pathological T stage*						
ypT0	7	29%	7	100%	NA	
ypT1	3	13%	NA		3	18%
ypT2	6	25%	NA		6	35%
ypT3	8	33%	NA		8	47%
Pathological N stage*						
ypN0	15	63%	6	86%	9	53%
ypN1	4	17%	1	14%	3	18%
ypN2	4	17%	0	0%	4	24%
ypN3	1	4%	0	0%	1	6%
Surgical approach						
Thoracolaparoscopic	18	75%	5	71%	13	76%
Laparoscopic transhiatal	5	21%	1	14%	4	24%
Open transthoracic	1	4%	1	14%	0	0%
Lymph node yield (median, IQR)	30	(19-36)	29	(23-40)	30	(19-35)
Positive lymph nodes harvested (median, IQR)	0	(0-1)	0	(0-0)	1	(0-3)

IQR interquartile range; *NA* not applicable; *pCR* pathologic complete response; *SD* standard deviation; *TRG* tumor regression grade
* Clinical and histopathologic T- and N-stage are based on UICC TNM 7th edition.
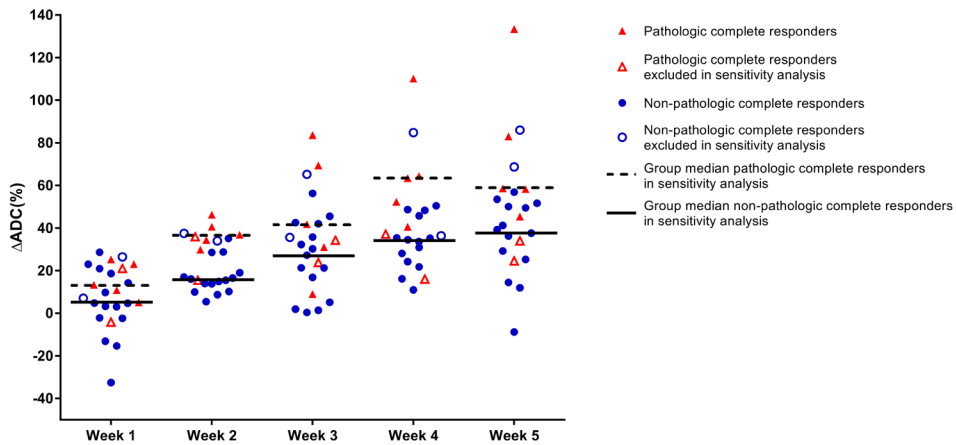
Figure 1. Relative changes in ADC values between baseline scans and scans during neoadjuvant chemoradiotherapy between pathologic complete responders (pCR, red triangles) and poor responders (non-pCR, blue circles). Patients who were excluded in the post-hoc sensitivity analysis are marked with an empty symbol.

ADC changes during nCRT

The relative increase in tumor ADC from baseline DW-MRI scans to scans acquired in the second week of nCRT (ΔADC_{week2}) was significantly associated with pCR (median [IQR]: 36% [30% – 41%] for pCR versus 16% [14% – 29%] for non-pCR, p = 0.004). In contrast, relative changes in ADC from baseline to DW-MRI scans acquired in the other weeks of nCRT were not significantly different between pCR and non-pCR groups (Table 2, Figure 1). Figure 2 presents baseline MRI scans and MRI scans in the second week of nCRT of a patient with pCR.

ROC curve analyses after ridge penalized regression analyses taking histology into account, demonstrated the highest c-statistic of 0.87 for the relative ADC increase from baseline to week 2 of nCRT (ΔADC_{week2}) combined with histology. Poorer discriminative ability was observed for histology alone (c-statistic: 0.67) or histology in combination with the $\Delta ADC(\%)$ of the other weeks (c-statistics: 0.73-0.80, Table 3, Figure 3). A predictive probability plot for pCR based on $\Delta ADC(\%)$ from baseline to week 2 for squamous cell carcinomas and adenocarcinomas is presented in Figure 4, demonstrating an increase in the probability for pCR when $\Delta ADC(\%)$ increases.

Sensitivity analyses

For the post-hoc sensitivity analysis, an additional 4 patients were excluded based on a delineated tumor volume on the baseline DW-MRI scan <7mL (n=3) and tumor histology other than adenocarcinoma or squamous cell carcinoma as based on the resection specimen

Figure 2. Patient with a cT3N2M0 distal esophageal squamous cell carcinoma with a pathologic complete response (pCR, TRG 1) to neoadjuvant chemoradiotherapy and a ΔADC_{week2} of 29%. T2 weighted images (**A** and **B**), diffusion-weighted images (b-value = 800 s/mm²) (**C** and D) and ADC maps (**E** and **F**) on a 1.5T MR scanner before (**A,C,E**) and in the second week of neoadjuvant chemoradiotherapy (**B,D,F**).

(n=1). In this study population of 20 patients, 5 patients had a pCR of which 2 adenocarcinomas and 3 squamous cell carcinomas. Exclusion of these additional 4 patients resulted in significant differences between patients with pCR and non-pCR in $\Delta ADC(\%)$ from baseline to weeks 2, 4 and 5 (Table 2). Furthermore, the c-statistics improved for the regression models with $\Delta ADC(\%)$ of weeks 1, 2, 3, 4 and 5 to 0.84, 0.97, 0.77, 0.93 and 0.90, respectively (Table 3).

Multiple imputation of the missing ADC value of week 4 and week 5 did not substantially impact the results of the regression analysis in terms of the observed c-statistics in the entire cohort (0.80 and 0.72 in the imputed datasets compared to 0.79 and 0.75 in the complete case datasets, respectively) or in the sensitivity analysis (0.93 and 0.87 in the imputed dataset compared to 0.93 and 0.90 in the complete case dataset, respectively) (Supplementary Table 2).

Table 2. Relative changes in ADC per week during neoadjuvant chemoradiotherapy between esophageal cancer patients with a pathologic complete response and non-pathologic complete response.

		Median ΔADC (%) (IQR)		
		pCR	**non-pCR**	**p-value***
Full cohort (n=24)	Week 1	13 (5, 23)	5 (-2, 19)	0.260
	Week 2	36 (30, 41)	16 (14, 29)	0.004
	Week 3	34 (24, 69)	30 (17, 42)	0.318
	Week 4	52 (37, 64)	35 (26, 47)	0.065
	Week 5	58 (34, 83)	40 (27, 53)	0.198
Sensitivity analyses (n=20)¥	Week 1	13 (11, 23)	5 (-2, 19)	0.098
	Week 2	37 (24, 41)	16 (10, 19)	0.001
	Week 3	42 (31, 69)	27 (5, 42)	0.168
	Week 4	63 (52, 64)	34 (24, 46)	0.002
	Week 5	59 (58, 83)	38 (25, 50)	0.003

ADC apparent diffusion coefficient; *IQR* interquartile range; *pCR* pathologic complete response
* p-value based on Mann-Whitney U test.
¥ After post-hoc exclusion of additional 4 patients based on baseline tumor volume delineated on DW-MRI <7 mL (n=3) and tumor histology other than adenocarcinoma or squamous cell carcinoma as based on the resection specimen (n=1).

Discussion

This prospective study was designed to assess the optimal timing of DW-MRI scanning during nCRT for prediction of pCR in esophageal cancer patients. The relative change in ADC (ΔADC) during the first 2 weeks of nCRT demonstrated the highest predictive ability for pCR at the time of surgery. This is of important clinical value as early response evaluation could enable individualized treatment regimens. Accurate assessment of response to nCRT is not only important for safe implementation of an organ-sparing approach in patients with pCR, but also to adapt treatment strategies in expected poor responders. Improving the accuracy of response evaluation after nCRT may provide improved outcomes for both patient groups.

In order to improve patient-friendliness of disease monitoring and (re)staging procedures, it is important to minimize the burden of these procedures. As demonstrated before, DW-MRI is generally well-tolerated by patients, although shorter acquisition times as well as altered body positioning could further improve patient experience.[39] Our results could further aid the minimization of the burden of repeated scanning for patients, as well as optimal usage of the available (financial) resources, while assuring the best predictive ability of DW-MRI.

Previous studies focusing on DW-MRI scanning in response prediction for esophageal cancer have mostly demonstrated promising findings regarding the predictive value of
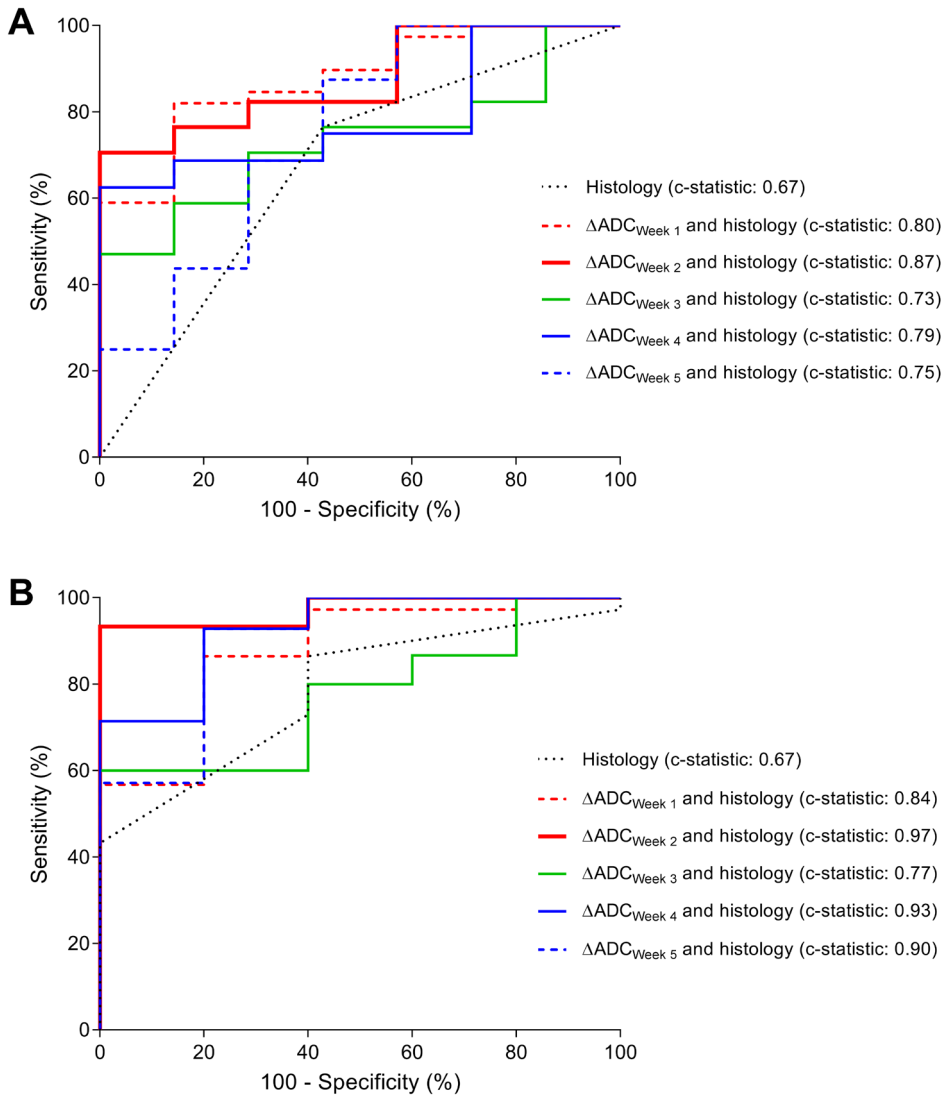
Figure 3. Receiver-operating-characteristic curve analysis for the regression models with relative changes in ADC per week, as well as histopathological tumor type, for discriminating between pCR and non-pCR patients in the full cohort (**A**) as well as in the sensitivity analysis (**B**).

ΔADC(%) for response prediction to nCRT.[14,15,18,40,41] The majority of these studies reported significant differences between responders and non-responders in ΔADC(%) from baseline to during nCRT,[14,15,24,41] whereas others report significant differences in ΔADC(%) from baseline to follow-up after nCRT.[18,41] Nevertheless, not all studies found the same predictive

Table 3. Ridge regression analyses demonstrating the discriminatory value of DW-MRI parameters per week with pathologic complete response (TRG 1) as outcome variable.

Intercept and predictors	Full cohort (n=24)			Sensitivity analyses (n=20)*		
	β	OR	c-statistic	β	OR	c-statistic
Histology						
Intercept	-1.00		0.67	-1.28		0.67
Squamous cell carcinoma¥	0.33	1.39		0.49	1.63	
Week 1						
Intercept	-1.74		0.80	-2.30		0.84
ΔADC$_{week1}$ (%)	0.04	1.04		0.06	1.06	
Squamous cell carcinoma¥	1.29	3.63		1.44	4.24	
Week 2						
Intercept	-3.45		0.87	-5.17		0.97
ΔADC$_{week2}$ (%)	0.09	1.09		0.15	1.16	
Squamous cell carcinoma¥	0.89	2.44		0.32	1.37	
Week 3						
Intercept	-1.09		0.73	-1.76		0.77
ΔADC$_{week3}$ (%)	0.00	1.00		0.02	1.02	
Squamous cell carcinoma¥	0.20	1.23		0.44	1.56	
Week 4						
Intercept	-1.61		0.79	-4.76		0.93
ΔADC$_{week4}$ (%)	0.01	1.01		0.08	1.08	
Squamous cell carcinoma¥	0.50	1.65		0.16	1.18	
Week 5						
Intercept	-1.57		0.75	-4.03		0.90
ΔADC$_{week5}$ (%)	0.01	1.01		0.06	1.06	
Squamous cell carcinoma¥	0.69	1.99		0.64	1.90	

ADC apparent diffusion coefficient; *c-statistic* concordance statistic; *OR* odds ratio; *pCR* pathologic complete response

Note. Due to rounding, the reported odds ratios might not precisely correspond with the reported beta regression coefficients.

* After post-hoc exclusion of additional 4 patients based on baseline tumor volume delineated on DW-MRI <7 mL (n=3) and tumor histology other than adenocarcinoma or squamous cell carcinoma as based on the resection specimen (n=1).

¥ Adenocarcinoma was used as reference category.

effect size, nor did they all report a significant relation between ΔADC(%) and response.[42,43] Several factors may account for these differences. First, ADCs were calculated based on different b-values varying from 0 and 1000[41], 0 and 600[24] to 0, 200 and 800.[14,15] The choice of b-values, number of signal averages (NSA's) per b-value, as well as the calculation of ADC values by various modeling strategies, are known to impact tumor ADC estimates.[21] Second, delineation methods for determining the volume of interest differ. Some studies consider the entire tumor volume as volume of interest,[14,15,18] whereas others only delineated the tumor on the most representative tumor slice.[41] Lastly, the nCRT regimen of choice varied between the studies.
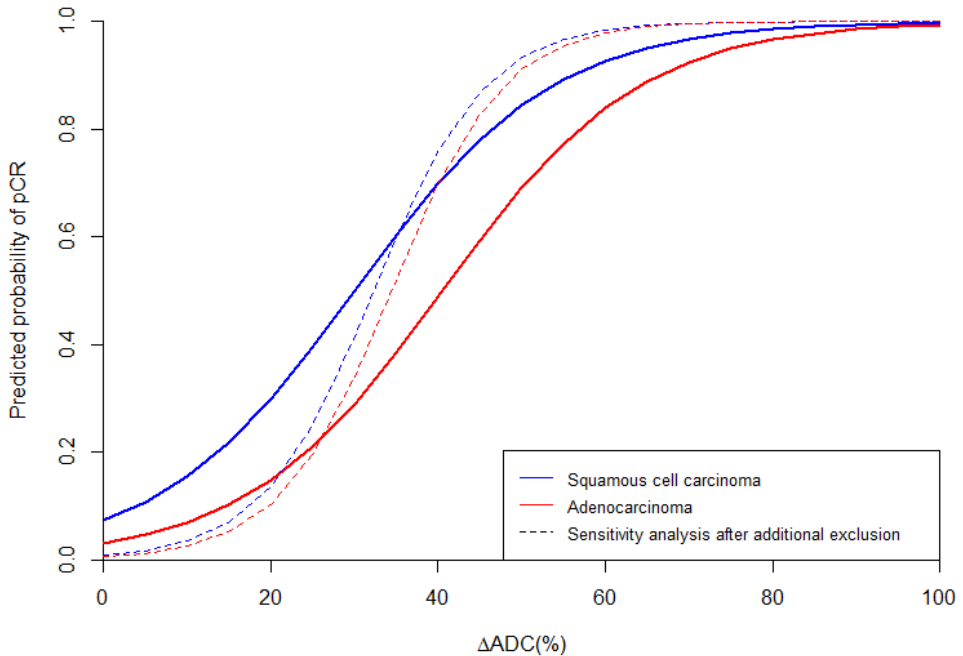
Figure 4. Predictive probability plot for pathologic complete response (pCR) based on the fitted regression model including relative changes in ADC (ΔADC(%)) from baseline to week 2 for squamous cell carcinomas (blue) and adenocarcinomas (red). The dashed lines represent the probability plot for the sensitivity analysis after additional exclusion of 4 patients.

Similar to our study, Wang et al.[24] performed weekly DW-MRI scanning during CRT in esophageal cancer patients to determine the optimal timing of response evaluation with DW-MRI. They also demonstrated DW-MRI scanning in the second or third week of CRT to be optimal for response assessment. As their study included only esophageal squamous cell carcinomas, used imaging response criteria as a reference standard (i.e. RECIST criteria[44] that assessed 52% of the patients to be a complete responder) instead of histopathology, used a different nCRT regimen (chemotherapy consisting of cisplatin with either 5-fluorouracil or paclitaxel, and radiotherapy consisting of 60 Gy in 30 fractions) and did not use ΔADC(%) but only single time point ADC values as measured, similar findings might not have been expected. Additionally, earlier studies by our group as well as the University of Texas MD Anderson Cancer Center that performed DW-MRI in the second or third week found these ΔADC(%) values to be highly predictive of response to nCRT.[14,15] Together, this supports the robustness of the findings from the current study.

The interobserver reproducibility of tumor delineation on DW-MRI and ADC measurements in esophageal cancer was shown to be very good by two previous studies, especially for the

semi-automated volumetric measurement method (intraclass correlation coefficient: 0.96, 95% CI: 0.91-0.98, p<0.001), which was also applied in the current study.[15,43] One of these studies compared manual delineation of a region of interest on the most representative tumor slice to semi-automatic delineation of the whole tumor volume, and found negligible differences in mean ADC measurements (between -0.25% and 0.31%).[15] A voxel-based analytical method, where changes in individual voxels can be monitored, may even provide more reliable results.[43] However, such an approach is challenging, since tumor regression is observed during nCRT and the esophagus is a moving organ[28], making spatial registration of DW-MRI obtained before and after start of nCRT complicated.

To improve external validity of our results, no cut-off values for ADC or ΔADC measurements for classification of complete responders versus non responders are reported in our study. Cut-off values are likely to be highly influenced by delineation techniques and determination of a 2D or 3D region of interest, as well as the b-values on which ADCs are calculated. To demonstrate this, we highlighted previously reported significant cut-off values for ΔADC(%), ADC_{mean} and ADC_{median} for discrimination of responders versus non-responders in the data of the current study in Supplementary Figure 3.

A recent meta-analysis demonstrated a pooled AUC of 0.91 (95% CI: 0.89-0.94) of ΔADC(%) values for treatment response prediction in esophageal cancer based on 4 studies.[40] We were not able to reproduce these results in our full cohort, but this cohort included 3 patients with small tumor volumes (<7 mL) and 1 patient who had a mixed adenoneuroendocrine carcinoma (MANEC) upon histopathological evaluation of the resection specimen. As MANECs are known to respond well to nCRT during treatment (which is reflected by an increase in ADC in the first weeks) but progress rapidly after completion, the inclusion of this patient clearly influenced the obtained results in this relatively small cohort.[45,46] Exclusion of the aforementioned patients dramatically improved the performance of ΔADC(%) for pCR prediction, resulting in a c-statistic of 0.97 for week 2. This also demonstrated that the predictive value of relative changes in ADC seems decreased for small tumors, which might be explained by the respiratory movement of the tumor during the DW-MRI scan. Typically, respiratory motion amplitudes of 1-2 cm are observed during scanning,[28,47] which might negatively impact the quantitative ADC assessment especially in small tumors. Improvement in pCR prediction in future studies may be obtained by incorporating motion management techniques.

Previous work has also demonstrated additional value of DCE-MRI, as well as PET-CT scanning in the prediction of treatment response in esophageal cancer patients.[15,48–52] Furthermore, emerging biomarkers such as circulating tumor DNA might further improve the predictive performance and might contribute to the safe investigation of an organ-sparing approach for predicted pCR to nCRT.

Significant strengths of the current study include the consistent use of one nCRT regimen

for all patients, the presence of a histopathologic reference standard in all patients, the inclusion of both squamous cell carcinomas and adenocarcinomas, as well as the consistent delineation by semi-automatic contouring. However, the specific hardware characteristics of the MR scanner and scan sequences, as well as the applied delineation technique and calculation of the ADC map by a mono-exponential model based on 3 b-values may limit the generalizability of the results. In addition, whole-tumor summary statistics (such as the mean ADC) are easily applicable, but fail to fully address the important issue of tumor heterogeneity.[21] Furthermore, the relatively small study population might have led to false-negative results (type II error) for differences in ΔADC(%) between responders and non-responders from baseline to the other weeks than week 2. Moreover, patients were included during a rather long study period of 2.5 years, since many eligible patients refused participation in this demanding and time-consuming study with weekly MRI scanning. However, the patients generally tolerated the MRI scans well (only 3 patients cancelled 1 MRI scan during their treatment in the entire cohort of 32 patients) and no adverse events occurred. Lastly, DW-MRI scanning is currently not routinely used in the staging of patients with esophageal cancer, which challenges the direct implementation of the results in clinical practice.

Future comparative studies should focus on further improving response evaluation after nCRT. In this regard, the recently started Dutch multicenter PRIDE study will further investigate the findings of the DW-MRI pilot studies in a larger patient cohort and aims at developing a multimodal clinically applicable prediction model.[53]

In conclusion, treatment-induced change in tumor ADC as measured on DW-MRI during the second week is most predictive for pCR to nCRT in esophageal squamous cell carcinoma and adenocarcinoma.

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SUPPLEMENTARY MATERIAL

Methods

Radiotherapy

All patients were treated with volumetric modulated arc radiotherapy. The gross target volume (GTV) was contoured based on information from the endoscopy and ^{18}F-FDG PET/CT scan. The extension of the GTV to the clinical target volume (CTV) was typically 3 cm cranially and caudally, and 0.5 cm circumferential without violation of anatomic boundaries. The planning target volume (PTV) expansion was 1 cm isotropically.

Image acquisition details

All images were acquired on a 1.5T Philips Ingenia (Best, the Netherlands), using anterior/posterior (28-channel) receive coils. Patients were positioned in supine position with both arms next to the body. Respiratory-triggered transverse anatomical T2-weighted scans (tT2W) were acquired with a multi-slice turbo spin echo sequence (TR/TE = 1604/100ms, resolution = 0.67x0.67x6.48mm^3). DW-MRI scans with 3 b-values (0, 200 and 800 s/mm^2) were acquired in coronal planes (number of squared averages [NSA] 4, 3 and 4 for b=0, 200 and 800 s/mm^2, respectively), using SPIR fat suppression and EPI read-out (resolution = 3.25x3.25x4mm^3, bandwidth per pixel = 22.9Hz) (see Supplementary Table 1). Images were obtained in coronal planes to mitigate the effects of respiratory motion on image quality, as it was demonstrated before that movement of the esophagus primarily occurs in the cranio-caudal direction.[1] As such, no out-of-plane motion will occur between the diffusion preparation and the image read-out.

Statistical analyses

Ridge regression is a penalized regression method, enabling reduction of model overfitting in a situation with few events per variable.[2] The applied overall penalty (λ_{min}) represents the minimum mean cross-validated error, which was obtained using 10-fold cross validation. Missing ADC values were imputed with using multiple imputation (multivariate imputation by chained equations, 20 imputed datasets with a maximum number of 20 iterations for each imputation).[3,4] All variables in Table 1 as well as the ADC statistics (mean, SD) of all weeks were used as predictor variables for the imputation. Subsequently, ΔADC(%) values were calculated and the ridge regression model was fitted on all imputed datasets. Model coefficients and the c-statistic were pooled using Rubin's rules.[5]

Supplementary Table 1. Image acquisition details.

General scanner characteristics		
Magnetic field strength		1.5 T
Vendor		Philips
Type		Ingenia
Protocol		
tT2W	Scan plane	transverse
	Scan mode	Multi-Slice
	Repetition time (ms)	1604
	Echo time (ms)	100
	Voxel size (mm)	0.67
	Slice thickness (mm)	6.48
	Flip angle	90
	Navigator	Yes
DWI	Scan plane	Coronal
	Scan mode	Multi-Slice
	Repetition time (ms)	4299
	Echo time (ms)	70
	Voxel size (mm)	3.25
	Slice thickness (mm)	4.0
	Flip angle	90
	b-values	0 / 200 / 800
	Number of squared averages	4 / 3 / 4
	Fat suppresion	SPIR
	Navigator	No

Supplementary Table 2. Ridge regression analyses demonstrating the discriminatory value of DW-MRI parameters per week with pathologic complete response (TRG 1) as outcome variable after multiple imputation (20 datasets) of the missing ADC values in week 4 and 5.

Full cohort (n=24)				Sensitivity analyses (n=20)*			
Intercept and predictors	β	OR	c-statistic	Intercept and predictors	β	OR	c-statistic
Week 4							
Intercept	-1.88		0.80	Intercept	-4.64		0.93
ΔADC_{week4} (%)	0.02	1.02		ΔADC_{week4} (%)	0.08	1.08	
Squamous cell carcinoma¥	0.65	1.92		Squamous cell carcinoma¥	0.21	1.23	
Week 5							
Intercept	-1.69		0.72	Intercept	-3.24		0.87
ΔADC_{week5} (%)	0.01	1.01		ΔADC_{week5} (%)	0.04	1.04	
Squamous cell carcinoma¥	0.66	1.94		Squamous cell carcinoma¥	0.36	1.43	

ADC apparent diffusion coefficient; *c-statistic* concordance statistic; *OR* odds ratio; *pCR* pathologic complete response

Note. Due to rounding, the reported odds ratios might not precisely correspond with the reported beta regression coefficients.

* After post-hoc exclusion of additional 4 patients based on baseline tumor volume delineated on DW-MRI <7ml (n=3) and tumor histology other than adenocarcinoma or squamous cell carcinoma as based on the resection specimen (n=1).

¥ Adenocarcinoma was used as reference category.
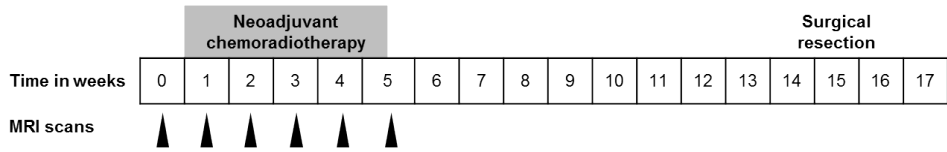
Supplementary Figure 1. Study design.
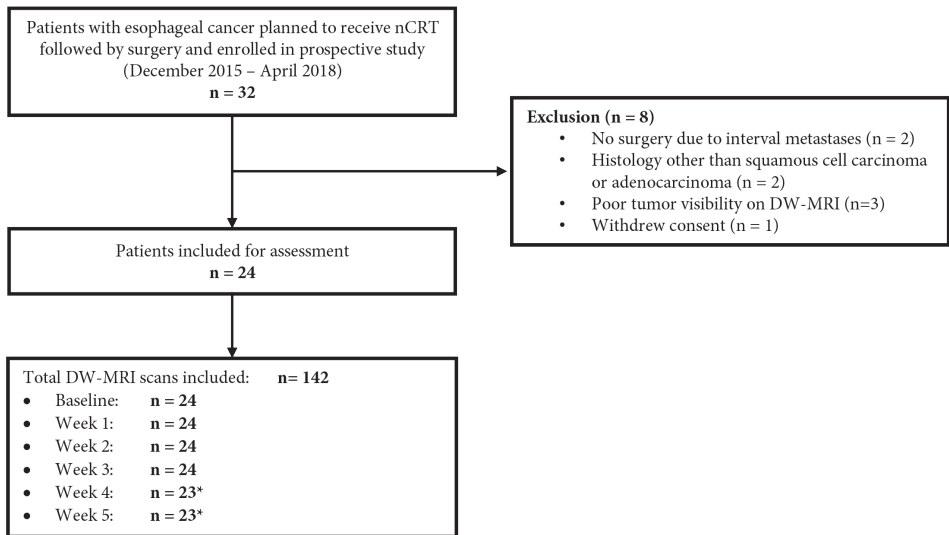
* Not available due to image acquisition problems (n = 1) or patients' refusal (n = 1)

Supplementary Figure 2. Flowchart.
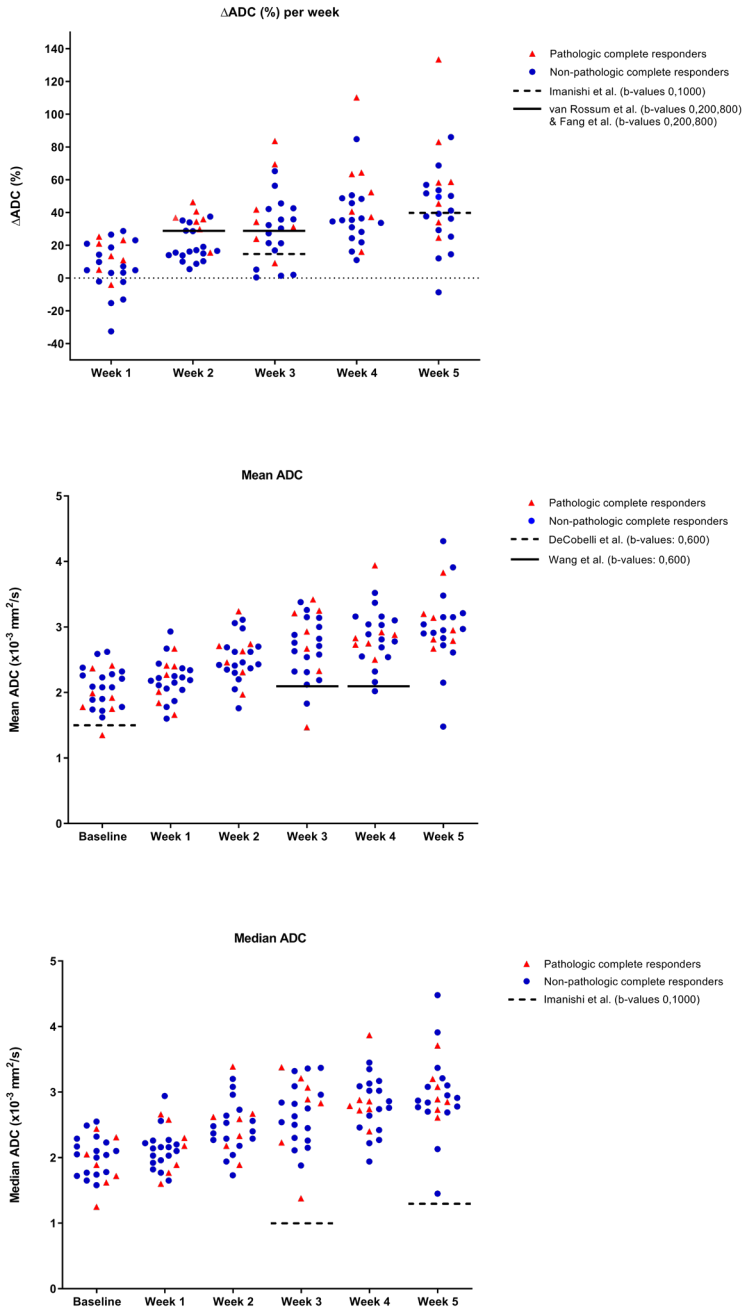
Supplementary Figure 3. Graphic illustration of ΔADC(%) and ADC cut-off points derived from the available literature (represented by the dashed and solid horizontal lines) on DW-MRI in pathologic complete response assessment for esophageal cancer and applied to the current data.

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6

Chapter 7

Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in esophageal cancer (PRIDE): a multicenter observational study

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Abstract

Background
Nearly one third of patients undergoing neoadjuvant chemoradiotherapy (nCRT) for locally advanced esophageal cancer have a pathologic complete response (pCR) of the primary tumor upon histopathological evaluation of the resection specimen. The primary aim of this study is to develop a model that predicts the probability of pCR to nCRT in esophageal cancer, based on diffusion-weighted magnetic resonance imaging (DW-MRI), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET-CT). Accurate response prediction could lead to a patient-tailored approach with omission of surgery in the future in case of predicted pCR or additional neoadjuvant treatment in case of non-pCR.

Methods
The PRIDE study is a prospective, single arm, observational multicenter study designed to develop a multimodal prediction model for histopathological response to nCRT for esophageal cancer. A total of 200 patients with locally advanced esophageal cancer - of which at least 130 patients with adenocarcinoma and at least 61 patients with squamous cell carcinoma - scheduled to receive nCRT followed by esophagectomy will be included. The primary modalities to be incorporated in the prediction model are quantitative parameters derived from MRI and ^{18}F-FDG PET-CT scans, which will be acquired at fixed intervals before, during and after nCRT. Secondary modalities include blood samples for analysis of the presence of circulating tumor DNA (ctDNA) at 3 time-points (before, during and after nCRT), and an endoscopy with (random) bite-on-bite biopsies of the primary tumor site and other suspected lesions in the esophagus as well as an endoscopic ultrasonography (EUS) with fine needle aspiration of suspected lymph nodes after finishing nCRT. The main study endpoint is the performance of the model for pCR prediction. Secondary endpoints include progression-free and overall survival.

Discussion
If the multimodal PRIDE concept provides high predictive performance for pCR, the results of this study will play an important role in accurate identification of esophageal cancer patients with a pCR to nCRT. These patients might benefit from a patient-tailored approach with omission of surgery in the future. Vice versa, patients with non-pCR might benefit from additional neoadjuvant treatment, or ineffective therapy could be stopped.

Trial registration: The article reports on a health care intervention on human participants and was prospectively registered on March 22, 2018 under ClinicalTrials.gov Identifier: NCT03474341.

Background

Esophageal cancer is the ninth most common type of cancer and the sixth most leading cause of cancer related death.[1] Surgical resection has long been the standard curative treatment for locally advanced esophageal cancer. However, the poor survival rates of surgery alone prompted many researchers to explore neoadjuvant therapy approaches to improve survival. Randomized clinical trials have demonstrated a consistent prognostic benefit of neoadjuvant chemotherapy or chemoradiotherapy followed by surgery over surgery alone for locally advanced esophageal cancer.[2–4] In the Netherlands, this resulted in the adoption of neoadjuvant chemoradiotherapy (nCRT) according to the CROSS regimen followed by surgery as standard of care.[4]

Nearly one third of all esophageal cancer patients (29%) treated with nCRT have no viable tumor cells detected at the primary tumor site at histopathological evaluation of the resection specimen, referred to as pathologic complete response (pCR).[4] It has been argued that in patients who achieve a pCR, surgery may be omitted without substantially reducing survival outcomes. In fact, as an esophagectomy is associated with substantial morbidity, mortality (up to 3-5%) and impaired quality of life[5–9], it can be speculated that surgery may have a detrimental effect on these patients. Consequently, proper identification of pathologic complete responders prior to surgery could yield an organ-preserving regimen avoiding esophagectomy and its postoperative complications.

Reversely, 18% of patients have more than 50% vital residual tumor cells in the primary tumor bed at histopathology after nCRT and surgery, referred to as non-responders.[4] The CROSS regimen is associated with grade ≥ 3 toxicity events according to the Common Terminology Criteria for Adverse Events (CTCAE) in up to 13% of patients.[4] Thus, these non-responders are exposed to side effects of nCRT probably without the benefits. Therefore, early identification of the non-responders during nCRT may be beneficial, as alternative treatment strategies could be explored for this group, such as additional neoadjuvant treatment, or ineffective therapy could be stopped.

Several diagnostic strategies have been proposed to predict response and ultimately omit surgery in selected patients. Computed tomography (CT) is used preferably in initial staging of esophageal cancer, especially with regard to the presence of distant metastases, but does not satisfactorily restage after nCRT (accuracies ranging from 51-75%).[10–12] Remaining tumor tissue is difficult to distinguish from therapy-induced peritumoral fibrosis and inflammation. As such, CT tends to overstage the preoperative tumor status.

Endoscopic ultrasonography (EUS) with or without biopsy has not yielded satisfactory results either. Systematic reviews pointed out that the accuracy rates of EUS for evaluating response to nCRT in esophageal cancer were moderate to poor (27-78%).[10,12,13] The pooled sensitivity of EUS after nCRT for detection of residual primary tumor in a meta-analysis

including 11 studies was 96.4% (95%-CI: 91.7%-98.5%), with a pooled specificity of only 10.9% (95%-CI: 3.5%-29.0%).[14] Endoscopic biopsy after chemoradiotherapy for esophageal cancer on the other hand was a very specific (pooled estimate 91.0%, 95%-CI: 85.6%-94.5%), but not a sensitive method (pooled estimate 34.5%, 95%-CI: 26.0%-44.1%) for detection of residual primary tumor after nCRT, as reported in a recent meta-analysis including 12 studies.[14] Results from the recently published preSANO study revealed that with bite-on-bite biopsies, the sensitivity for the detection of residual disease increased substantially compared to regular biopsies (an increase from 54% [95%-CI: 38%-70%] to 74% [95%-CI: 64%-83%]).[15]

Moreover, promising results for response prediction were obtained using repeated integrated ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (^{18}F-FDG PET-CT), with accuracies ranging from 76% to 85%.[10,16–18] The change in ^{18}F-FDG uptake during nCRT, reflecting a change in glucose metabolism by cancer cells, may be used to identify these responders.[16] A systematic review on the value of these quantitative ^{18}F-FDG PET(-CT) measurements including 20 studies, showed that response could be predicted with sensitivities ranging from 33% to 100% (pooled estimate of 67%) and specificities ranging from 30% to 100% (pooled estimate of 68%).[16]

This supports the concept that functional imaging could play an important role in accurate response prediction. In this light, magnetic resonance imaging (MRI) has recently shown great potential for response prediction to nCRT for esophageal cancer.[19–22] Diffusion-weighted MRI (DW-MRI) is a functional imaging modality that allows for tissue characterization by deriving image contrast from restriction in the free diffusion (i.e. random mobility or Brownian motion) of water molecules, which is related to microstructural tissue organization. An apparent diffusion coefficient (ADC) map can be derived from the DW-MRI images to quantify the diffusion restriction in a certain volume of interest. The ADC is inversely correlated with tissue cellularity. As chemoradiotherapy can result in the loss of cell membrane integrity, tumor response can be detected as an increase in tumor ADC. In two exploratory studies, the treatment-induced relative changes in ADC over time (ΔADC), during nCRT, appeared highly predictive of histopathological response.[21,23] Using repeated DW-MRI only, a high area under the receiver operating curve (AUC_{ROC}) was attained for identifying pathologic complete responders.[21,23]

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), the acquisition of serial MR images while intravenously administering a contrast agent, provides further insight into the nature of the tissue properties related to perfusion. Based on these images, quantitative parameters such as the transfer constant (K^{trans}) and blood-normalized initial-area-under-the-gadolinium-concentration curve (AUC) can be calculated. The AUC reflects blood flow, vascular permeability and the fraction of interstitial space.[24] In a pilot study, all pathologic complete responders showed a decrease in AUC of 25% or more over the entire

treatment course (ΔAUC), whereas an increase in AUC during treatment was observed for those patients who did not obtain a pCR (*p*=0.003).[25]

In addition to functional imaging, circulating tumor cells and corresponding circulating tumor DNA (ctDNA) have been proposed as noninvasive and real-time biomarkers for predicting patient prognosis in esophageal carcinomas.[26–29] Circulating tumor cells and ctDNA are present in the blood vessels adjacent to the tumor, and are subsequently transported throughout the body via the circulation.[28] As such, ctDNA reflects the presence of disease and could provide valuable information on the response to treatment. Since ctDNA can be detected from regular peripheral blood samples, the detection of ctDNA could be a promising, minimally invasive addition to the evaluation of treatment response and prognosis in esophageal cancer patients.

Study aim

As the aforementioned modalities do not individually fulfill the requirements to justify treatment decision making, the primary aim of the current study is to develop a multimodal prediction model that predicts the patients' individual probability of a pCR after nCRT for esophageal cancer. Accurate prediction of the response to nCRT could lead to a patient-tailored approach with omission of surgery in the future in case of predicted pCR, potentially improving quality of life and reducing health care costs. Furthermore, additional neoadjuvant treatment could be offered to patients in case of non-pCR.

Methods

Objectives

The primary objective of the study is to develop a multimodal prediction model that predicts a patients' individual probability of a pathologic complete response to nCRT in esophageal cancer by integrating DW-MRI, DCE-MRI and ^{18}F-FDG PET-CT scans acquired prior to, during and after administration of nCRT.

The secondary objectives are as follows:

- To evaluate the accuracy of the multimodal prediction model as developed under the primary objective for the prediction of a pathologic good response (i.e. tumor regression grade [TRG] 1 or TRG2).
- To evaluate the effectiveness and efficacy of an endoscopic and endosonographic assessment after nCRT for the detection of residual disease, in relation to the response classification as predicted by the model developed under the primary objective.
- To evaluate the presence of, and changes in, ctDNA during nCRT as a biomarker for a patients' response to nCRT, the detection of residual disease after nCRT and progression-free and overall survival.

- To evaluate the accuracy of the multimodal prediction model as developed under the primary objective with addition of the endoscopic and endosonographic assessment, and the ctDNA measurements for the prediction of pCR and pathologic good response (i.e. TRG1 or TRG2).
- To evaluate the accuracy of a visual assessment for the detection of residual disease after nCRT based on MRI and ^{18}F-FDG PET-CT.
- To evaluate the performance of MRI and ^{18}F-FDG PET-CT imaging parameters for the prediction of progression-free and overall survival.

Study design

The PRIDE study is a prospective, multi-center observational study with participation of 4 high-volume centers in the Netherlands (University Medical Center Utrecht, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, University Medical Center Groningen and Amsterdam University Medical Centers). Patients will be informed and included at the outpatient department at one of these investigational centers. The study has been approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (17-941, NL62881.041.17). All participating hospitals gave their consent after assessment of local feasibility. Written, voluntary, informed consent to participate in the study will be obtained from all patients.

Study population

In order to be eligible to participate in this study, a patient must be scheduled to receive nCRT for a potentially resectable, locally advanced (cT1b-4aN0-3M0) esophageal or gastroesophageal junction tumor, either squamous cell carcinoma or adenocarcinoma. Neoadjuvant chemoradiotherapy will be delivered according to the CROSS-regimen[4], consisting of weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg per milliliter per minute) and paclitaxel (50 mg per square meter of body-surface area) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, delivered 5 days per week on workdays with intensity modulated radiotherapy) followed by esophagectomy after 8-10 weeks. Primary diagnosis and staging will be based on endoscopy, EUS, ^{18}F-FDG PET-CT and histopathological evaluation of a tumor biopsy.

Patients who meet exclusion criteria for MRI or for intravenous gadolinium-based contrast, patients with a blood plasma glucose concentration >10 mmol/L or poorly controlled diabetes mellitus, patients with a status after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of the primary tumor prior to the start of nCRT, patients younger than 18 years and pregnant or breast-feeding patients are not eligible.

Study protocol

A schematic representation of the study protocol is depicted in Figure 1. Patients will undergo standard diagnostic work-up and staging for esophageal cancer, including a baseline ^{18}F-FDG PET-CT (PET-CT$_{pre}$). After informed consent and before the start of nCRT, a baseline MRI (MRI$_{pre}$) is performed. A second MRI (MRI$_{per}$) and ^{18}F-FDG PET-CT (PET-CT$_{per}$) will be performed during the third week of nCRT (after 10-15 fractions of radiotherapy). A third MRI (MRI$_{post}$) will be performed 6-8 weeks after the completion of nCRT, and no sooner than within 2 weeks before the intended date of surgery. The third ^{18}F-FDG PET-CT (PET-CT$_{post}$) is usual care in all participating centers, and will be performed within the same timeframe as the MRI$_{post}$. Blood samples will be acquired at 3 time points, i.e. before, during and after nCRT, to evaluate the presence of, and changes in circulating tumor DNA (ctDNA). Furthermore, patients will be asked to undergo an additional endoscopic assessment after nCRT, PET-CT$_{post}$ and MRI$_{post}$, within 2 weeks prior to surgery. Surgical resection will be performed 8-10 weeks after completion of nCRT.
In summary, for study purposes patients will undergo 3 additional MRI scans (MRI$_{pre}$, MRI$_{per}$, MRI$_{post}$), 1 additional ^{18}F-FDG PET-CT scan (PET-CT$_{per}$), blood samples at 3 time points and 1 postchemoradiation endoscopic and endosonographic assessment. The ^{18}F-FDG PET-CT scans before start of nCRT and after nCRT (PET-CT$_{pre}$ and PET-CT$_{post}$) are standard of care in all participating centers and will also be used for study purposes. All study related procedures will take place before surgery.

MRI

Patients will undergo anatomical (T2-weighted [T2W]) and functional MRI (DWI and DCE) in one scanning session every time. Two DWI series and one DCE scan will be acquired. The sagittal DWI series (sagittal intravoxel incoherent motion [sIVIM] with 13 b-values: 0, 10, 20, 30, 40, 50, 75, 100, 200, 350, 500, 650 and 800 s/mm^2) will be used for quantitative analyses but also for the visual assessment. Transversal DWI series (high resolution tDWI, b-values: 0 and 800 s/mm^2) will mostly be used for visual assessments. The DCE-MRI scans will be acquired with a temporal resolution of 3 seconds and the injection of a gadolinium-based contrast agent. ADC and AUC values of the various time points will be used as quantitative measures of the DWI and DCE series, respectively. Extensive effort has been put in the standardization of MRI scan sequences by imaging experts and the exchange of test scans.

^{18}F-FDG PET-CT

The PET-CT examinations will be performed according to EARL guidelines (European Association of Nuclear Medicine)[30]. ^{18}F-FDG is the tracer that will be used for the assessment of abnormal glucose metabolism in the tumor. On the ^{18}F-FDG PET-CT scans, standardized

Figure 1. Study design

uptake volumes (SUV_{max}, SUV_{mean}) and the total lesion glycolysis (TLG) will be measured to quantify changes over time in the glucose metabolism of the tumor.

Postchemoradiation endoscopic assessment

Patients will be asked to undergo a postchemoradiation endoscopic assessment, consisting of an additional endoscopy with (random) bite-on-bite biopsies of the primary tumor site and other suspected lesions in the esophagus, as well as endosonography with fine needle aspiration of suspected lymph nodes after completion of nCRT. This is an optional study procedure and patients can choose to opt-out for this additional procedure.

The endoscopic reevaluation will be performed by 1 or 2 experts in each of the 4 centers, to ensure high quality and uniform procedures and to reduce the impact of operator dependency. Furthermore, video recordings of all patients with negative biopsies that showed visual abnormalities of any kind during the endoscopic procedure will be reevaluated by an expert panel that will be blinded for the pathological outcome of the resection specimen in order to investigate whether a qualitative assessment of an expert team can help to correctly identify residual tumor in patients with a negative biopsy.

Blood samples

Blood samples will be used to evaluate the presence of ctDNA and changes in ctDNA concentrations since the release of ctDNA within a patient during the course of chemoradiotherapy has recently been demonstrated to be a dynamic process.[31] To allow molecular analysis of liquid biopsies, blood will be collected in cell-free DNA collection tubes. The plasma will be aliquoted after 2 centrifugation steps and will be stored at -80°C.[32] This will allow isolation of ctDNA and subsequent mutation analysis by means of Next Generation Sequencing (NGS) at a later stage.

Surgery

A transthoracic or transhiatal esophagectomy will be performed in all patients, depending on patient characteristics, tumor localization, and local preference. Open, hybrid and completely minimally invasive techniques are allowed. Resection of the primary tumor and regional lymph nodes will be carried out according to the current requirements for esophageal cancer surgery in The Netherlands.[33] For correct TNM-staging, the lymph node dissection should contain at least 15 nodes derived from both the mediastinum and upper abdomen.

Histopathological assessment

The resection specimen will be evaluated meticulously according to a standardized protocol (tumor type and extension, lymph nodes, resection margins) by a dedicated pathologist with gastrointestinal subspecialty in each center. The pathologist will be blinded for the

results of the MRI and PET-CT exams. The most recent edition of the UICC (International Union Against Cancer) protocol will be used for TNM-classification and stage grouping.[34] Special attention will be given to reporting the effects of nCRT in the resection specimen. The (estimated) location of the primary lesion plus surrounding areas and other suspected lesions in the esophagus will be embedded in order to adequately judge the presence of residual tumor and treatment effects. The percentage of viable tumor cells will be scored microscopically (ranging from 0-100%), which directly corresponds to a stage in either of the two most often used grading systems: 'TRG 1 to 4'[35] or the 'Mandard score 1 to 5'[36]. Therapy effects include necrosis, inflammation with multinucleated giant cells, fibrosis and calcifications. Fibrosis is the most remarkable effect and is used to estimate the extension of the tumor before treatment. Lastly, all resection specimens with TRG 1-2 will be revised by a second expert pathologist.

Follow-up

Patients will remain in follow-up for five years after surgery, according to local follow-up policies. The general follow-up guideline in the Netherlands consists of routine follow-up visits every 3 months during the first year after surgery. In the second year, follow-up takes place every 6 months, and then yearly until 5 years after surgery. Diagnostic investigations are generally only performed on indication.[33]

Study outcomes

The primary outcome of this study is the performance of the multimodal prediction model for the correct prediction of a patients' individual probability of a pCR to nCRT based on DW-MRI, DCE-MRI and ^{18}F-FDG PET-CT scans acquired prior to, during and after administration of nCRT. Secondary outcome parameters include the performance of the model for good response (i.e. TRG1 and TRG2), the effectiveness and efficacy of a postchemoradiation endoscopic and endosonographic assessment for pCR prediction, the value of ctDNA as a biomarker for a patients' response to nCRT, progression-free and overall survival, the performance of the model including results from the endoscopic and endosonographic assessment and ctDNA measurements for pCR and good response prediction, the performance of a visual assessment for the detection of pCR after nCRT based on MRI and ^{18}F-FDG PET-CT, and lastly the performance of the model for prediction of progression-free and overall survival.

Statistical analysis

Data analysis of primary study objective

The analysis regarding the primary objective of this project will have pCR as the predicted outcome of interest. Statistical analysis and reporting will be performed in accordance with

the Standards for the Reporting of Diagnostic accuracy studies (STARD) statement, and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[37,38]. The assessor(s) of the MRI and PET-CT images will be blinded for the histopathological outcome.

A multivariable logistic regression model will be developed with pCR as dichotomous outcome measure. Many of the imaging parameters are likely highly correlated and provide similar (non-additional) information, particularly within one modality. The most valuable imaging parameters within one imaging modality (i.e. within DW-MRI, DCE-MRI and PET-CT imaging parameters) will be entered in the model, based on the results of previous knowledge. To determine whether the imaging modalities provide complementary value in the prediction of pCR, models will be compared based on Akaike's Information Criterion (AIC).

Model discrimination and calibration results will be evaluated for the multivariable logistic regression models using receiver operating characteristic (ROC) curve analysis with area-under-the-curve (AUC_{ROC}) estimates and visual inspection of model calibration plots, respectively. Internal validation using the bootstrap method with 1000 repetitions will be carried out to provide insight into potential over-fitting and optimism in model performance. Bootstrapping will allow for calculation of bias-corrected c-indexes of the prediction model, and provides shrinkage factors that can be used to adjust the estimated regression coefficients in the model for overfitting and miscalibration. Sensitivity analyses will be performed excluding one participating center each time to study the influence of the multicenter study design on the model performance.

Data analysis of secondary study objectives
ROC curve analysis with AUC_{ROC} estimates will be used to determine the additional value of the postchemoradiation endoscopic and endosonographic assessment and the ctDNA measurements to the model as developed under the primary objective, as well as the accuracy of the multimodal prediction model for the prediction of pathologic good response (i.e. combined TRG1 and TRG2).

The performance of a visual assessment for the detection of pCR after nCRT will be analyzed by calculation of diagnostic performance measures such as sensitivity, specificity, positive predictive value, negative predictive value and accuracy (including corresponding 95% confidence intervals). This also applies to the individual performance of the endoscopic and endosonographic assessment for the detection residual disease, as well as for the performance of ctDNA measurements.

Multivariable Cox regression models will be used to analyze the performance of the prediction model as developed under the primary objective, MRI and ^{18}F-FDG PET-CT imaging parameters, and ctDNA measurements for the prediction of progression-free and overall survival.

Sample size calculation

It is conservatively assumed that adenocarcinoma and squamous cell carcinoma need separate modeling and a priori stratification. Based on 3 independent imaging predictors (e.g. a DW-MRI imaging parameter such as ΔADC, a DCE-MRI imaging parameter such as ΔAUC and a ^{18}F-FDG PET-CT imaging parameter such as ΔSUV_{max}), this requires 30 events for both histopathological subtypes, according to the '1 predictor per ~10 events' rule-of-thumb in logistic regression analysis.[39,40] The CROSS-trial demonstrated a pCR rate of 23% and 49% after nCRT for patients with adenocarcinomas and squamous-cell carcinomas respectively.[4] According to the 1 in 10 rule, this translates in a total accrual of at least 130 adenocarcinoma patients and at least 61 squamous-cell carcinoma patients. In case of an unexpected aberrant distribution of patients that leads to decreased pCR rates, the aim is an accrual of 200 patients.

Discussion

Currently, groups of patients with esophageal cancer fit in certain protocolled treatment approaches, but the treatment is rarely a perfect fit for the individual patient. The PRIDE study investigates whether a multimodal image-guided model can be developed that accurately predicts a patients' individual histopathological response to nCRT. Such a model would enable personalized treatment for patients with esophageal cancer. Recent studies indicate that an organ-sparing approach might be feasible in selected patients with esophageal cancer who have a pCR after nCRT.[41–43] However, satisfactory diagnostic strategies to select these pathologic complete responders are lacking up to now. Therefore, surgical resection after nCRT remains the most optimal curative treatment in terms of survival in patients with locally advanced esophageal cancer. If the PRIDE concept provides high predictive performance for pCR, this could potentially lead to a new standard of care with direct benefits to esophageal cancer patients. Furthermore, accurate identification of the non-responders may be beneficial, as these patients might benefit from alternative treatment strategies, such as additional neoadjuvant treatment, or ineffective therapy could be stopped in this group.

In the current study protocol, strict time points are chosen for the MRI and ^{18}F-FDG PET-CT imaging, as well as for the blood samples and endoscopic assessment. This way, a homogeneous cohort will be created, in which measurement variability will be reduced as much as possible. This is also reflected in the extensive effort of the participating centers to standardize the imaging protocols.

Since therapy effects continue to develop after treatment, previous studies have underlined that MRI and PET-CT imaging during nCRT as well as after nCRT for esophageal cancer

can function as predictors for pCR.[10,18,25,21,44,45] As such, the MRI_{post} and $PET-CT_{post}$ scans should be as close to the histopathological assessment of the outcome (pCR) as possible, in order to make sure that the findings on the MRI_{post} and $PET-CT_{post}$ will represent the histopathology accurately. This will likely also prevent false positive results caused by transient radiation-induced esophagitis, which is known to decrease over time after nCRT. Therefore, the chosen time points in our study include scans before the start of nCRT (MRI_{pre} / $PET-CT_{pre}$), scans during the third week of nCRT (MRI_{per} / $PET-CT_{per}$), and scans within 2 weeks before surgery (MRI_{post} / $PET-CT_{post}$). In patients undergoing an additional endoscopic and endosonographic assessment, this will be intended after the ^{18}F-FDG PET-CT_{post} and the MRI_{post}, but prior to surgery. If an organ-sparing approach is eventually implemented in clinical practice for predicted complete responders, an endoscopic confirmation without signs of residual tumor will most likely be required.

Of note, two studies, namely the Dutch SANO trial[46] and the French ESOSTRATE trial (ClinicalTrials.gov identifier NCT02551458), are currently studying active surveillance strategies after nCRT for patients with a clinical complete response. For the SANO trial, a clinical complete response is based on ^{18}F-FDG PET-CT and endoscopy with at least 8 (random) bite-on-bite biopsies. These studies together will include a total of 600 patients (300 within each trial) and the primary outcome of these studies is survival. In contrast to these trials, the current study involves the careful development of an accurate image-guided response evaluation strategy to predict pCR in an observational study, without the simultaneous implementation of postponed surgical resection in clinical complete responders that might harm the patient. The results of this study will therefore play an important role in the accurate identification of esophageal cancer patients with a pCR to nCRT who could benefit from an organ-sparing approach in the future. Ultimately, the results of the three trials together could lead to a patient-tailored wait-and-see approach with omission of surgery in the appropriate patients.

7

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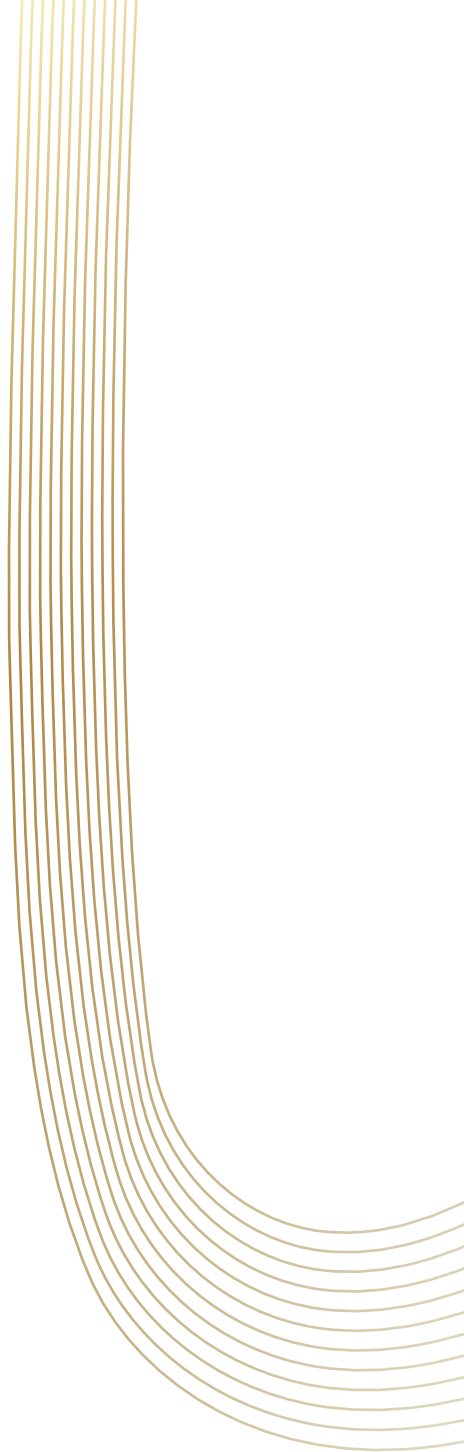
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Patient perspectives on repeated MRI and PET/CT examinations during neoadjuvant treatment of esophageal cancer

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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.

8

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 2).[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).

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 3), 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.

Table 1. 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

Table 2. 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

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 6 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).

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).

8

Perceived burden during MRI and PET/CT scanning

*: 1 = none → 5 = very much
§: 1 = absolutely not → 5 = absolutely yes
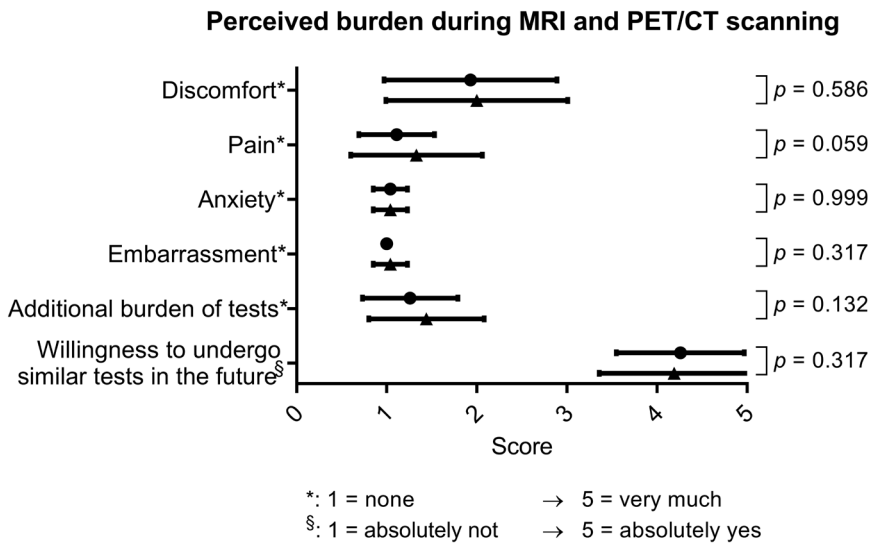
Figure 1. Perceived burden by the patients during MRI and PET/CT scanning

Table 3. 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

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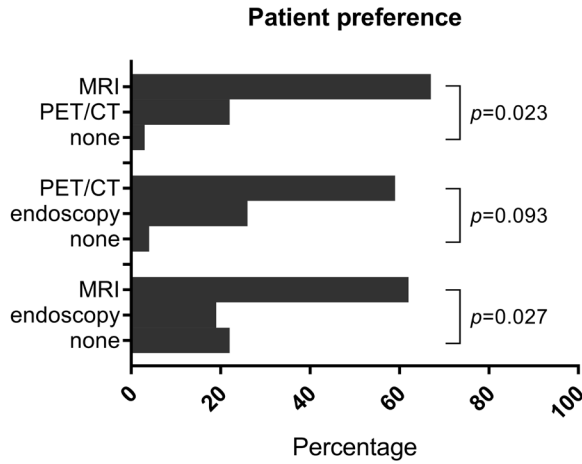
Figure 2. Comparative module forcing patients to rank the different tests from least to most inconvenient

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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Surgical treatment

Surgical treatment in the era of multimodality management of esophageal cancer

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Joint first authorship

Abstract

Over the last decades, the treatment of resectable esophageal cancer has evolved into a multidisciplinary process in which all players are essential to be successful. Medical oncologists and radiation oncologists are increasingly involved since the implementation of neoadjuvant therapy, which has shown to improve survival. Although esophagectomy is still considered the cornerstone of curative treatment for locally advanced esophageal cancer, it remains associated with considerable postoperative morbidity, despite promising results of minimally invasive techniques. In this light, both physical status and response to neoadjuvant therapy may be important factors for selecting patients who will benefit from surgery. Furthermore, it is important to optimize the entire perioperative trajectory: from the initial outpatient clinic visit to postoperative discharge. Enhanced Recovery After Surgery (ERAS) is increasingly recognized for esophagectomy and emphasizes perioperative aspects such as nutrition, physiotherapy, and pain management. To date, several facets of esophageal cancer treatment remain topic of debate, such as the preferred neoadjuvant treatment, anastomotic technique, extent of lymphadenectomy, organization of postoperative care and the role of surgery beyond locally advanced disease. This review aims to describe the current and future perspectives in the surgical treatment of patients with esophageal cancer in the context of available literature.

Introduction

The management of esophageal cancer is complex, and highly variable between countries and centers. Multimodality treatment, which implies neoadjuvant chemoradiotherapy or perioperative chemotherapy in combination with esophageal resection, is increasingly applied over the world, since it has shown a survival benefit over surgery alone.[1–4] Treatment teams nowadays not only consist of a surgeon, but are truly multidisciplinary with the participation of medical oncologists, radiation oncologists, gastroenterologists, dieticians and physiotherapists. Although the role of perioperative treatment has significantly evolved with the introduction of neoadjuvant and adjuvant treatment strategies, there is general international consensus that surgery remains a fundamental part of the curative treatment of locally advanced esophageal cancer.[1]

This review summarizes the advances in surgical treatment in the era of multimodality management of esophageal cancer. The first section gives an overview of patient selection for surgery and perioperative therapy. The second section addresses commonly used surgical techniques for esophageal cancer, with a particular focus on minimally invasive surgery, anastomotic techniques, the extent of lymphadenectomy, and the role of surgery in advanced disease. Finally, the introduction of enhanced recovery protocols after esophagectomy is discussed.

Patient selection for surgery

Esophagectomy is a highly complex surgical procedure that is associated with relatively high morbidity, mortality and recurrence rates.[1] The eligibility of a patient for surgical resection strongly depends on the extent of the disease, as well as on the general condition of the patient. Decisions on the initial treatment approach of esophageal cancer are based on clinical staging, which should be carried out with the utmost accuracy.[2] Adequate staging at least includes a complete clinical examination and a computed tomography (CT) scan of the neck, chest and abdomen.[1,5] Furthermore, to determine whether lymphatic or distant metastatic disease is present in patients with more advanced tumors that are candidates for surgical resection, endoscopic ultrasound (EUS) and ^{18}F fluorodeoxyglucose positron emission tomography-CT (PET-CT) should be performed.[1,2,6,7] A multidisciplinary team is then necessary for choosing the appropriate treatment for each patient individually, not only based on the previously mentioned tumor stage, but also depending on tumor location, histological subtype, comorbidities and age. In general, patients with locally advanced disease (cT1N+ and cT2-4aN0-3), are potential candidates for neoadjuvant treatment followed by surgical resection.

In patients with early esophageal cancer (high-grade dysplasia [Tis], mucosal [T1a], and submucosal cancer [T1b]), endoscopic therapy (endoscopic mucosal resection as well as endoscopic submucosal dissection) is highly successful and functions as the preferred therapeutic approach.[2,8,9] Depending on several histopathological parameters of the resected specimen, such as irradicality, the presence of lymfovascular invasion, deeper submucosal tumor invasion or poor differentiation, subsequent surgical resection is indicated.[1,10,11] In patients not eligible for surgery, endoscopic therapy followed by chemotherapy or chemoradiotherapy might be considered as alternative treatment.

In addition to tumor stage, the location of the esophageal tumor influences a patients' eligibility for surgical resection. Especially patients with proximal esophageal tumors are usually poor candidates for surgery because of limitations in surgical techniques (e.g., confined working space and poor overview).[12] Furthermore, due to its anatomical proximity to the hypopharynx, surgery includes a combined pharyngo-laryngo-esophagectomy in some cases, resulting in permanent tracheostomy and impacting the quality of life of these patients enormously.[13] Thus, these patients frequently depend on definitive chemoradiotherapy with encouraging 3-year outcomes and acceptable toxicity.[13]

Comorbidity

Accurate patient selection for surgery does not only depend on tumor characteristics, but also on assessment of comorbidities, a patients' nutritional status and cardiopulmonary function.

Results of a large population based study showed that a substantial percentage of patients diagnosed with esophageal cancer has a history of hypertension (56%), congestive heart failure (21%), smoking (71%), and diabetes mellitus (18%).[14] This is reflected in the majority of patients having an American Society of Anesthesiologists (ASA) score of 3 (65%).[14] From a cohort of 1057 patients that underwent transthoracic esophagectomy, only 31.6% (n=334) fulfilled the criteria of a low comorbidity status (ASA score ≤2, WHO/ECOG score ≤1, age ≤65 years, body mass index (BMI) 19-29kg/m^2).[15]

The previously mentioned comorbidities are well known risk factors for several postoperative complications. For example, anastomotic leakage is associated with pre-existent cardiovascular disease such as heart failure, coronary artery disease, peripheral vascular disease and hypertension.[14] In the context of risk factor evaluation, a patients' vascular status can be objectively evaluated by arterial calcification on a computed tomography (CT) scan. Patients with arterial calcifications have a higher risk of developing anastomotic leakage and esophageal conduit necrosis after esophagectomy compared to patients without calcifications.[16–19] Preoperative identification of these high-risk patients could aid in selecting patients that would potentially benefit from ischemic conditioning of the gastric conduit to reduce anastomotic leakage rates.[20,21]

Some studies suggest that diabetes mellitus is associated with impaired anastomotic healing and therewith increases the risk of anastomotic leakage after esophagectomy. However, this relation has not been consistently described in literature. A recent review and meta-analysis including 16 observational studies concluded that diabetes mellitus was significantly associated with an increased risk of anastomotic leakage after esophagectomy (OR: 1.63; 95% CI: 1.25-2.12; p<0.001).[22] Interestingly, in subgroup analyses, this association was mainly found in surgical populations from Europe and America (OR: 1.42; 95% CI: 1.22-1.65; p<0.001) but not in Asian populations (OR: 2.27; 95% CI: 0.86-6.05; p=0.1).[22] The authors hypothesized that the limited number of included studies - with only 1540 Asian patients - was more likely to result in a weakened persuasive power of their pooled estimates.[22]

Preoperative pulmonary function (reflected in the forced expiratory volume for 1 second expressed as percentage of the forced vital capacity percent (FEV1%) and peak expiratory flow) is also associated with major complications after esophagectomy.[23,24] Pulmonary complications can be reduced by minimally invasive surgery, thoracic epidural analgesia and early enteral nutrition.[25] Other strategies to improve preoperative condition of the patient include physical therapy to increase cardiorespiratory function.[26,27] A systematic review including 12 studies evaluating the effects of preoperative exercise therapy on postoperative complication rate and length of hospital stay concluded that preoperative exercise therapy can be effective for reducing postoperative complication rates and length of hospital stay after cardiac or abdominal surgery.[28] The effect of preoperative inspiratory muscle training on the incidence of postoperative pneumonia in patients undergoing esophagectomy was studied in a multicenter randomized controlled trial (the PREPARE study), of which the results will be published in the near future.[29]

As far as patients that are not surgical candidates are concerned, definitive chemoradiotherapy functions as a suitable alternative to surgical resection.[1]

Age

Age has historically functioned as a selection criterion for treatment and management in cancer patients. The association of age with severity of complications after esophagectomy is demonstrated by an adjusted OR of 1.02 per year increase in age (95% CI: 1.00-1.04, p=0.014).[23] However, age itself might not influence postoperative outcomes as much as assumed. Age ≥80 years is currently related to a decreased likelihood of esophagectomy compared to definitive chemotherapy (OR: 0.79, 95% CI 0.65-0.96, p<0.015), as well as a decreased likelihood of palliative therapy versus no treatment (OR: 0.73, 95% CI 0.65-0.81, p<0.001) and a decreased likelihood of trimodality therapy compared to definitive chemoradiation (OR: 0.15, 95% CI 0.12-0.18, p<0.001) using taking persons between 70 and 79 years of age as a reference category.[30] In this same series, all therapies were associated

9

with improved survival in older age. Thus, old age should not be the only reason to exclude patients from surgical treatment that might improve survival.[31] Treatment decisions should be made individually and with appropriate caution in older patients. A preoperative geriatric assessment is advisable to obtain a holistic view of the patient, which can give insight in the risk of postoperative complications, such as delirium.[32]

Perioperative treatment for locally advanced esophageal cancer

For locally advanced disease (cT1N+ and cT2-4aN0-3), treatment practices vary around the globe. However, there is a worldwide consensus that surgery alone should no longer be the standard of care for treatment of these tumors.[33] Over the last decades, numerous strategies have been evaluated to improve the treatment results by adding perioperative or neoadjuvant chemo(radio)therapy to surgical resection. The MAGIC study[4] and French FNCLCC/FFCD 9703 study[34] were the first to show an overall survival benefit for perioperative chemotherapy in patients with lower esophageal, GEJ and gastric adenocarcinoma. After these results, the CROSS study combined carboplatin/paclitaxel with 41.4 Gy radiation and demonstrated a 14% increase in 5 year overall survival for patients with esophageal cancer (both squamous cell carcinoma and adenocarcinoma) treated with neoadjuvant chemoradiotherapy followed by surgery compared to surgery alone.[3,35] However, the recently presented phase III FLOT 4 trial has shown that the FLOT regimen (docetaxel, oxaliplatin, leucovorin, and 5-FU) improves the outcome of patients with esophageal adenocarcinoma and locoregional disease as compared to the ECF/ECX triplet (epirubicin, cisplatin, and 5-FU or capecitabine).[36] Currently, several randomized trials comparing perioperative chemotherapy and neoadjuvant chemoradiotherapy are being undertaken. The NeoAegis study[37] compares CROSS versus MAGIC and the German ESOPEC study compares FLOT versus CROSS in patients with esophageal adenocarcinoma[38]. The Chinese CMISG1701 study compares overall survival between neoadjuvant chemotherapy (cisplatin/paclitaxel) with neoadjuvant chemoradiotherapy (cisplatin/paclitaxel with 40 Gy radiation), both followed by esophagectomy for locally advanced resectable esophageal squamous cell carcinoma.[39] The NEOSCOPE study investigates whether induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin, both combined with 45 Gy radiation, is superior as pre-operative regimen in pathological complete response of resectable esophageal adenocarcinoma.[40] Lastly, the PROTECT-1402 study compares 3 cycles of FOLFOX combined with concurrent radiotherapy (41.4 Gy) or carboplatin and paclitaxel with the same radiation regimen for esophageal and junctional cancer.[41] An overview of these studies (including ClinicalTrials.gov identifiers) is presented in Table 1.

Besides chemotherapy and radiation treatment, targeted therapies are emerging. Patients with esophageal adenocarcinoma should be tested for overexpression of the human epidermal growth factor receptor 2 (HER2) protein on the tumor biopsy.[1] If a high level of HER2 expression is identified, HER2 antibodies such as trastuzumab and pertuzumab could be added to perioperative or neoadjuvant therapy (RTOG 1010 phase III study NCT01196390, PETRARCA phase II/III study NCT02581462, INNOVATION phase II study NCT02205047, TRAP phase Ib study NCT02120911).[33] Another targeted therapy includes the addition of a vascular endothelial growth factor receptor (VEGFR)-2 antibody, ramucirumab, that interacts with the angiogenic pathway in tumorgenesis.[33] Its value is currently assessed in patients with HER2-negative GEJ and gastric adenocarcinoma (RAMSES phase II/III study NCT02661971). Moreover, the addition of immunotherapeutic strategies to neoadjuvant chemoradiation or perioperative chemotherapy is currently evaluated, such as programmed death ligand 1 (PD-L1) targeted therapy with atezolizumab or pembrolizumab (PERFECT phase II study NCT03087864, KEYNOTE-590 phase III study NCT03189719).

From the adjuvant perspective, chemotherapy and radiotherapy have not been integral parts of the treatment of resectable esophageal cancer. A recent network meta-analysis demonstrated that, in contrast to surgeryi combined with neoadjuvant therapy, surgery combined with adjuvant therapies appeared lesser effective and showed no survival advantage when compared with surgery alone (HR: 0.87, 95% CI 0.67-1.14, p=0.321).[42] Furthermore, adjuvant chemotherapy after neoadjuvant chemoradiotherapy followed by surgery did not provide additional benefit for esophageal cancer patients without residual disease (ypT0N0, HR: 0.82, 95% CI 0.50-1.35) or without non-nodal residual disease (ypT+N0, HR: 0.93, 95% CI 0.74-1.17).[43] Yet, in patients with residual nodal disease (ypTanyN+), adjuvant chemotherapy may provide a survival benefit (HR: 0.70, 95% CI 0.57-0.85).[43] However, since this has not been investigated in a formal randomized controlled trial, further research is needed before routine application in clinical practice.

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Complete responders to neoadjuvant therapy

As a pathologic complete response to neoadjuvant therapy is observed in a substantial part of patients (up to 23% of patients with an adenocarcinoma and 49% of patients with a squamous cell carcinoma following neoadjuvant chemoradiotherapy[3]), it is argued that these patients may not benefit from subsequent surgery.[44] Patients with a pathologic complete response have a favorable prognosis with a lower risk of developing a local regional recurrence and an increased survival compared to other subgroups.[35,45–48] Several studies have been initiated to preoperatively identify these patients for an organ-preserving approach, avoiding unnecessary surgery related morbidity, followed by active surveillance.

Table 1. Overview of neoadjuvant and perioperative treatment studies for esophageal cancer

Study	Comparison	Experimental treatment
Perioperative chemotherapy		
MAGIC[35]	Perioperative chemotherapy versus surgery	ECF
FNCLCC/FFCD 9703[36]	Perioperative chemotherapy versus surgery	Cisplatin/fluorouracil
FLOT4 trial (NCT01216644)	Comparison of two perioperative chemotherapy regimens	FLOT ECF/ECX
Neoadjuvant chemoradiotherapy		
CROSS[3,37]	Neoadjuvant chemoradiotherapy versus surgery	Carboplatin/paclitaxel and 41.4 Gy
NeoAegis (NCT01726452)	Neoadjuvant chemoradiotherapy versus perioperative chemotherapy	Carboplatin/paclitaxel and 41.4 Gy ECF
ESOPEC (NCT02509286)	Neoadjuvant chemoradiotherapy versus perioperative chemotherapy	Carboplatin/paclitaxel and 41.4 Gy FLOT
CMISG1701 (NCT03001596)	Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy	Cisplatin/paclitaxel and 40 Gy Cisplatin/paclitaxel
PROTECT-1402 (NCT02359968)	Comparison of two chemotherapy regimens, both with concurrent radiotherapy	Carboplatin/paclitaxel and 41.4 Gy FOLFOX and 41.4 Gy
NEOSCOPE (NCT01843829)	Induction chemotherapy (oxaliplatin/capecitabine) followed by a comparison of two preoperative chemoradiotherapy regimens	Carboplatin/paclitaxel and 45 Gy Oxaliplatin/capecitabine and 45 Gy
Immunotherapies		
RTOG 1010 (NCT01196390)	HER-2 antibodies in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel (radiation dose not specified)	Trastuzumab
PETRARCA (NCT02581462)	HER-2 antibodies in addition to perioperative chemotherapy with FLOT	Trastuzumab and pertuzumab
INNOVATION (NCT02205047)	HER-2 antibodies in addition to perioperative chemotherapy with cisplatin/capecitabine or cisplatin/5-fluorouracil	Trastuzumab Trastuzumab and pertuzumab
TRAP (NCT02120911)	HER-2 antibodies in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel and 41.4 Gy	Trastuzumab and pertuzumab

RAMSES (NCT02661971)	VEGFR-2 antibody treatment in addition to perioperative chemotherapy with FLOT	Ramucirumab
PERFECT (NCT03087864)	PD-L1 targeted therapy in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel and 41.4 Gy	Atezolizumab
KEYNOTE-590 (NCT03189719)	PD-L1 targeted therapy in addition to perioperative chemotherapy with cisplatin/5-FU	Pembrolizumab

ECF epirubicin, cisplatin and fluorouracil; *ECX* epirubicin, cisplatin and capecitabine; *FLOT* fluorouracil, leucovorin, oxaliplatin and docetaxel; *FOLFOX* fluorouracil, oxaliplatin, folonic acid; *Gy* Gray; *HER2* human epidermal growth factor receptor 2; *PD-L1* programmed death ligand 1; *VEGFR2* vascular endothelial growth factor receptor2

Note. All studies with ClinicalTrials.gov identifiers are currently enrolling patients or awaiting results.

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In this light, various diagnostic strategies such as endoscopic biopsies and/or EUS,[49] 18F-FDG PET(-CT),[50,51] diffusion weighted (DW)[52–55] and dynamic contrast enhanced (DCE)[56] magnetic resonance imaging (MRI) are being researched to predict response and ultimately avoid surgery in selected patients. The MUNICON-1[57] and MUNICON-2 trials[58] have shown that PET-based therapy individualization could be a feasible approach for GEJ adenocarcinomas. Furthermore, at least four large trials (recruiting ≥ 200 patients) are currently studying the accuracy of various diagnostic modalities for pathologic complete response assessment and/or the safety of active surveillance after a complete clinical response (the French ESOSTRATE trial [NCT02551458], the Korean ESOPRESSO trial [NCT01740375], the Dutch PRIDE study and the Dutch SANO trial [Netherlands Trial Register ID NTR6803]).

Enhanced Recovery After Esophagectomy in the preoperative setting

The principles of Enhanced Recovery After Surgery (ERAS) were developed in 2001 by a group of surgeons who later established the ERAS Society.[59] Since then, the ERAS Society has published various evidence-based multidisciplinary guidelines that aim to minimize the surgical stress response (minimally invasive techniques, carbohydrate loading), facilitate early postoperative mobilization (minimum number of drains, regional analgesia), and stimulate early postoperative resumption of oral intake. Although ERAS guidelines were published for several gastro-intestinal surgical procedures including colonic surgery, pancreaticoduodenectomy, rectal surgery, bariatric surgery, and gastrectomy, consensus is lacking regarding the optimal approach to patients undergoing esophagectomy.[60–65] While the composition of the optimal perioperative care pathway remains subject of debate for

Table 2. Essential elements of Enhanced Recovery After Esophagectomy

At the outpatient clinic	Structured multidisciplinary counseling
	Evaluation and optimization of the nutritional state
	Stimulation of smoking and alcohol cessation
	Possibly inspiratory muscle training
Shortly before surgery	Avoidance of prolonged fasting
	Carbohydrate loading
During surgery	Minimally invasive surgical techniques
After surgery	Stimulation of early postoperative mobilization
	Adequate pain management
	Limitation of drains, lines, and catheters
	Possibly early resumption of oral intake

esophagectomy, several enhanced recovery protocols have been suggested with some reporting a median length of hospital stay of 8 days.[66,67] Key elements of an Enhanced Recovery After Esophagectomy program can be found in Table 2.

Outpatient clinic

In the pre-admission phase, structured counseling by a multidisciplinary team is considered key to preparing patients for surgery. First, this increases information retention and offers the possibility correct potential misconceptions about disease and treatment, which can reduce patient anxiety.[68,69] Second, the time between diagnosis and surgery can be used to evaluate and monitor the nutritional state, which is at risk of deteriorating in esophageal cancer patients. At time of diagnosis, most esophageal cancer patients are malnourished due to local tumor effects causing dysphagia, anorexia, and cancer related cachexia.[70] Weight loss and nutritional deficiencies are further increased by toxicities related to neoadjuvant therapy. Since malnutrition is in turn associated with an increased risk of postoperative infectious complications, nutritional screening is advised in all patients prior to esophagectomy.[66,71–76]

According to the latest guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), nutritional intervention is indicated for patients who are at severe nutritional risk (i.e., >10-15% weight loss within 6 months, BMI <18.5 kg/m^2, Subjective Global Assessment Grade C, or serum albumin <30 g/L without evidence of hepatic or renal dysfunction).[77,78] Nutritional intervention should involve nutrition support with sip feeds, enteral tube feeding, or parenteral feeding, in that order of preference.[77,78]

Various methods for nutritional intervention during neoadjuvant therapy prior to esophagectomy are summarized in a recently published review.[70] All included studies showed that esophageal stents can be successfully used to palliate dysphagia, although the overall stent migration rate in these patients is 29.9%.[70] Instead of stenting to allow oral intake, enteral feeding can be initiated through a nasoduodenal, nasojejunal, or jejunostomy tube. Since long periods of nasoduodenal or nasojejunal tube feeding can be discomforting for patients, some surgeons advocate laparoscopic placement of a feeding jejunostomy at an early stage prior to esophagectomy.[79] Studies on laparoscopically inserted jejunostomies were all of retrospective nature, and demonstrated an increase in weight ranging from 0.4 to 11.8 kg.[70] Only one comparative study was included in the previously mentioned review that compared esophageal stenting to jejunostomy feeding, which reported no significant difference between the two groups with respect to complication rates (22% for esophageal stenting versus 14% for jejunostomy, p=0.11) or weight gain (4.4 kg for esophageal stenting versus 4.2 kg for jejunostomy, p=0.59).[70] The optimal nutritional approach for patients with resectable esophageal cancer undergoing neoadjuvant treatment prior to esophagectomy has thus to be found.

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Lastly, if applicable, patients should be encouraged and supported to cease alcohol abuse and smoking during the pre-admission phase, which reduces the risk of postoperative complications.[80,81]

Before surgery

Shortly before esophagectomy, ERAS aims to minimize the surgical stress response and thereby decrease insulin resistance, which may reduce postoperative morbidity and length of hospital stay.[82–84] In this context, ingestion of an oral carbohydrate solution is advised prior to esophagectomy as it is believed to cause an initial increase in baseline insulin sensitivity and in that way dampen surgery-induced insulin resistance.[84] Although randomized controlled trials were inconsistent, a recent meta-analysis of studies including a variety of surgical procedures indicated that carbohydrate loading may be associated with a reduced length of hospital stay when compared to placebo or fasting.[85,86] While the reported carbohydrate doses are varying, an amount of 400 mL 12.5% carbohydrate solution may be advised.[78] With regard to the latter, it must be noted that prolonged preoperative fasting should be avoided to reduce patient discomfort and prevent the body from entering a catabolic state that aggravates the surgical stress response.[87,88] The traditional practice of fasting from midnight before surgery was based on the doctrine that this would reduce the risk of aspiration during the induction anesthesia, which was based on old and sparse literature.[82,89,90] Convincing evidence has emerged that ingestion of solid foods until 6 hours and clear liquids until 2 hours before elective surgery is safe, which led to adaptation of the ASA guidelines.[91,92] These eased limitations can most likely also be applied to esophagectomy, although cautiousness is warranted in patients with dysphagia as they may have an increased risk of aspiration.[66,78]

Minimally invasive surgery

Traditional open esophagectomy (OE) is a highly invasive procedure that is associated with considerable morbidity.[93–95] Over the last decades, minimally invasive techniques are increasingly adopted for esophageal surgery.[96] An important aim of minimally invasive surgery is to reduce the physiological stress response to trauma, which can in turn diminish postoperative immunosuppression and susceptibility to infections.[97,98] Additionally, laparoscopic and thoracoscopic procedures are generally associated with less pain when compared to their open alternatives, which promotes recovery.[99–101] In this context, minimally invasive esophagectomy (MIE) was introduced in the 1990's and found to be a safe alternative to OE in various studies.[102,103] The term MIE is used to describe an esophagectomy procedure that avoids the invasiveness of thoracotomy and laparotomy by

performing thoracoscopy and laparoscopy, respectively. Although the worldwide implementation of MIE is at an advanced stage, only one randomized controlled trial was conducted to compare MIE to OE so far (i.e., the TIME trial).[96,104] Patients were included from 5 high-volume centers (>30 esophagectomies per year) and MIE was significantly associated with fewer postoperative pulmonary infections during hospitalization (12% versus 34%) and within 2 weeks after surgery (9% versus 29%), less blood loss (median 200 versus 475 mL), shorter hospitalization (median 11 versus 14 days), lower pain scores during the first 10 postoperative days (median Visual Analogue Scale 2 versus 3), and better short-term quality of life scores when compared to OE.[104] As no differences were found regarding 3-year overall and disease-free survival, the results from this study suggest that MIE provides short-term advantages while maintaining oncological standards.[104,105]

Despite promising results for MIE, recent population-based studies did not unequivocally support its superiority over OE.[106–109] While the length of hospitalization was repeatedly shown to be shorter for MIE, pulmonary complications and overall morbidity were generally equal.[106–109] Moreover, a higher re-operation rate was consistently reported for MIE in these studies.[106–109] The authors postulated that this might be attributable to a learning effect, as MIE is a relatively novel and technically complex procedure that is still in its implementation phase.[107] A recent retrospective multicenter study investigated the learning curve for MIE and found that a plateau is reached after 119 cases, based on the evaluation of anastomotic leakage rates when making a transition from a cervical to an intrathoracic anastomosis.[110] As the mean anastomotic leakage rate decreased from 18.8% (first time quintile) to 4.5% (fifth time quintile) during this time period, it appears that patients are exposed to additional risks during the learning phase.[110]

The thoracoscopic part of MIE is particularly difficult to master, especially when performing an intrathoracic anastomosis. A hybrid procedure, which avoids the need for a technically challenging thoracoscopic phase, has been proposed and investigated in a multicenter trial (i.e., the MIRO trial).[111] Patients were randomly allocated to receive either hybrid (laparoscopy and thoracotomy) or open (laparotomy and thoracotomy) esophagectomy with an intrathoracic anastomosis.[111] Although the full results were not made available yet, major pulmonary complications were reported to be significantly less frequent in the hybrid group (30.1% versus 17.7%) in a recently published abstract by the American Society of Clinical Oncology.[112] In combination with several case-matched studies, these findings suggest that morbidity may already be reduced by only performing the abdominal phase minimally invasive.[113,114] In this light, hybrid esophagectomy might be an option for surgeons in low-volume centers that would face challenges in completing their thoracoscopic learning phase due to insufficient caseload. However, the additional value of avoiding an open thoracic phase has not yet properly been investigated and therefore comparative studies for full versus hybrid MIE are warranted. A pilot trial was conducted to investigate the

9

feasibility of a randomized three-armed study that compares open versus hybrid versus full MIE.[115] As patient recruitment was achieved rapidly, this trial is currently continued into a definitive randomized controlled trial.

In attempt to overcome the technical challenges of MIE, robot-assisted minimally invasive esophagectomy (RAMIE) was introduced in 2003.[116] Robotic assistance allows for more natural hand movements and provides an enhanced three-dimensional vision of the surgical field.[117] 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. Since its introduction, RAMIE has been shown to be a safe and oncologically adequate alternative to OE and conventional MIE.[116–118] Furthermore, with its technical advantages, RAMIE may be an option for patients who were traditionally deemed inoperable due to a tumor or lymph node metastasis in the upper mediastinum. In a recent prospective study, 31 patients with an upper mediastinal tumor (cranial border at 18-24 cm from the incisors) or lymph node metastasis (level 2 and/or 4) underwent RAMIE and the authors concluded that the technique is feasible for this patient group, although it was associated with relatively high mortality (i.e., 10%).[119] More research is needed regarding the clinical merits and possibly extended operability criteria of RAMIE. The ROBOT-trial, which compared RAMIE to OE in terms of short-term surgical and oncological outcomes, will be published soon.[120]

Anastomotic techniques

After esophagectomy for cancer, the gastrointestinal continuity is most commonly restored by gastric tube reconstruction with an esophagogastric anastomosis. Several anastomotic techniques are available to construct an esophagogastrostomy. In this section, postoperative morbidity and mortality, functional results, and oncologic outcomes of various commonly used anastomotic techniques are described.

Cervical versus intrathoracic anastomosis

During esophagectomy for cancer either the lowest part of the thoracic esophagus is resected followed by an intrathoracic esophagogastric anastomosis high in the chest, or the whole thoracic esophagus is resected combined with a part of the cervical esophagus followed by a cervical esophagogastric anastomosis. Both intrathoracic and cervical anastomoses are commonly performed worldwide, although the first is increasingly applied.[96]

So far, 4 randomized trials have assessed clinical outcomes after either an intrathoracic or cervical anastomosis.[121–124] In one of these clinical trials, the intrathoracic anastomosis was

significantly associated with a lower anastomotic leakage rate when compared to the cervical anastomosis.[121] Although the other three clinical trials did not report a statistical significant difference in leakage rates between the two methods[122–124], two of these suggested a non-significant difference in leakage rates in favor of an intrathoracic anastomosis.[123,124] This difference was confirmed by two meta-analyses – including all four clinical trials – that concluded that an intrathoracic anastomosis could be associated with lower anastomotic leakage rates (pooled leakage risk: 13.6% versus 2.9%[125],[126] for the cervical versus intrathoracic anastomosis, respectively). However, the evidence of the currently available clinical trials is limited because they all included a limited number of patients (32-92 patients per study) with few events (2-13 events per study), leading to uncertain estimates.[121,124,127,128] In this regard, three large population based studies – including 2086[129], 2944[130] and 2969[14] patients – confirmed that an intrathoracic anastomosis is associated with lower leakage rates and shorter hospital stay. Reported factors that may explain the lower leakage rate associated with an intrathoracic anastomosis include less tissue ischemia due to the shorter distance the blood supply must travel and less risk of tension on the anastomosis.[14,126]

Although leakage rates from the intrathoracic anastomosis may be lower, some surgeons prefer an cervical anastomosis because the sequelae of cervical anastomotic leakage are claimed to be less severe.[131] It is hypothesized that cervical anastomotic leakage can be easily diverted by opening the neck wound and therewith prevent mediastinal contamination. However, the studies that support this hypothesis are rare , and included a limited number of patients.[132,133] Furthermore, it should not be underestimated that cervical anastomotic leakage can also lead to severe intrathoracic complications (pleural empyema and mediastinal abscess) occurring in up to 62% of patients.[134,135] To this regard, a previously mentioned meta-analysis and two large population based studies found no difference regarding in-hospital mortality between cervical and intrathoracic anastomoses.[126,129,136] However, one of these studies indicated that length of intensive care stay and length of hospital stay was longer in patients after an intrathoracic anastomotic leakage.[129] This suggests that the clinical course of anastomotic leakage is indeed more severe for intrathoracic anastomoses, but that this does not increase the risk of postoperative mortality.

Prevention of adverse events (i.e., recurrent laryngeal nerve palsy and stricture formation) leading to subsequent functional complaints (i.e., impaired swallowing and dysphagia) - after esophagectomy is important because it can impair quality of life. In this context, a meta-analysis of clinical trials and a large population-based study assessed recurrent laryngeal nerve palsy rates after esophagectomy, and found that an intrathoracic anastomosis is associated with a statistically significant lower incidence of recurrent nerve trauma.[126] This is likely explained by the close anatomical relation of the recurrent laryngeal nerve

9

with the esophagus in the cervical region. Regarding benign strictures requiring dilatation, none of the 4 conducted clinical trials and the two subsequent meta-analysis reported a difference in the incidence between the cervical and intrathoracic anastomotic approach.[121–126] It should be noted, however, that fair comparison of trials is restricted due to the lack of consensus regarding definition, diagnostic criteria, and threshold of treatment for anastomotic strictures.

Oncologic outcomes after esophageal surgery may also be influenced by the choice of anatomic location of the anastomosis, as a cervical anastomosis allows for a higher proximal resection margin. In this regard, one trial reported a statistically significantly higher irradical resection rate in in patients after an intrathoracic anastomosis compared to those receiving a cervical anastomosis (33% versus 10%, respectively; p<.05).[124] Two other trials and a large population based study that also reported on this finding did not find a difference in radical resection rates.[121,122,129] Patient selection remains important in this context, as patients with supracarinal tumors are likely not eligible for an intrathoracic anastomosis. However, owing to neoadjuvant chemoradiotherapy, an intrathoracic anastomosis is likely safe in patients with infracarinal tumors.[137]

In summary, based on the current available evidence an intrathoracic anastomosis is associated with reduced anastomotic leakage rates and recurrent nerve paresis rates compared to a cervical anastomosis. However, the currently available clinical studies are limited by their moderate quality and relatively small sample size. Currently a randomized controlled trial is underway in order to demonstrate whether a minimally invasive cervical or intrathoracic anastomosis should be preferred for patients with infracarinal esophageal tumors (the ICAN trial[138]).

Hand-sewn versus stapled anastomosis

Hand-sewn anastomosis and stapled anastomosis with a mechanical device are the most commonly used methods to construct an esophagogastric anastomosis. At present, the choice of a hand-sewn or stapled anastomosis mostly depends on the preference of the surgeon. So far, 10 clinical trials have been published that compared the hand sewing technique with the stapling technique for the esophagogastric anastomosis.[124,128,139–146] In none of these clinical trials a statistically significant difference in the incidence of anastomotic leakage was reported.[139–146] This finding was confirmed by two meta-analyses that did not find a difference in postoperative anastomotic leakage rates, other complications and postoperative mortality between hand-sewn or stapled anastomosis.[147,148] Although, it has been suggested in a subgroup analysis of 302 patients that the stapled approach may reduce anastomotic leakage rates compared to a single-layer hand-sewn esophagogastric anastomosis (RR: 0.37, 95% CI: 0.18-0.76, p<0.01).[147]

In two of the 10 clinical trials that compared the stapled and hand-sewn method, a

statistically significant higher anastomotic stricture rate was found after stapled anastomotic construction.[142,146] The other eight clinical trials did not report a difference in anastomotic strictures rates,[139–141,143–145] although one study reported a non-significant difference towards more strictures in the stapled-group.[143] A meta-analysis which included 7 of the 10 clinical trials found that a stapled anastomosis was associated with a higher anastomotic stricture rate (OR: 1.76, 95% CI, 1.09–2.86; p=0.02).[148] A possible explanation for this higher stricture rate is that the compression of tissue in the stapling device results in tissue ischemia between the staples, leading to fibrosis.

In summary, the current evidence suggests that hand-sewn and stapled anastomoses are equally safe with regard to leakage rates, other complications, and postoperative mortality. However, stapled anastomoses are likely associated with more stricture formation when compared to hand-sewn anastomoses.

Lymphadenectomy for esophageal cancer

Lymph node status is an important prognostic factor in esophageal carcinoma and an independent predictor of survival.[149,150] Therefore, lymph node dissection is considered to be an integral part of oncological surgery. For esophagectomy, a transthoracic approach is generally considered to be optimal in oncological terms, as it allows for two-field lymphadenectomy with upper mediastinal dissection.[94,151] The alternative, transhiatal esophagectomy, was designed to reduce post-operative morbidity and mortality by avoiding thoracotomy and is therefore often reserved for patients with considerable comorbidity and high risk of complications following a potential thoracotomy.[152] A prospective randomized study comparing a transhiatal resection with an extended transthoracic approach for mid and distal esophageal adenocarcinomas showed that median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups.[93,153] However, there was a trend reported towards improved long-term survival at 5 years with the extended transthoracic approach (51% for transthoracic approach versus 37% for the transhiatal approach in type I esophageal adenocarcinoma).[93,153] Especially patients with 1 to 8 positive lymph nodes in the resection specimen showed a 5-year locoregional disease-free survival advantage if operated via the transthoracic route compared to the transhiatal approach (23% versus 64%, p=0.02).[153]

A higher lymph node yield was associated with improved survival in an international cohort of 2303 esophageal cancer patients that underwent surgery alone.[154] In contrast, two studies that performed post-hoc analyses on lymph node yield in patients treated with chemoradiotherapy followed by esophagectomy, suggested that lymph node yield was not associated with survival.[155,156] It should be noted however, that these findings have to be

9

interpreted with caution and the debate on the benefit of extensive lymphadenectomy has not yet been settled. It is well known that more lymph nodes are resected with a transthoracic approach compared to a transhiatal approach in patients that undergo surgery alone as well as neoadjuvant chemoradiation followed by surgery.[157] In a recently published post-hoc analysis of a randomized controlled trial, a more favorable prognosis for the transthoracic approach was found in patients who underwent surgery alone, especially in patients with a limited number of positive lymph nodes.[157] This benefit was absent in patients who underwent nCRT[157], however this might be due to a lack of power for this post-hoc analysis. A recent population-based study from The Netherlands including 2698 esophageal cancer patients that underwent neoadjuvant chemoradiotherapy contradicted these results, and found a significant association between lymph node yield during esophagectomy and increased overall survival.[158] In subgroup analyses of patients with squamous cell carcinoma and adenocarcinoma, cN0 and cN+, transthoracic and transhiatal approaches, and ypN0 and ypN+, a high lymph node yield remained significantly associated with increased overall survival.[158]

Moreover, a more extensive lymphadenectomy reflected by a higher lymph node yield during esophagectomy does not seem to decrease patients' short- and long-term health related quality of life, as reported by a Swedish population-based study including a total of 616 patients.[159]

Taken together, there is no evidence to date that justifies reduction in the quality or the extent of lymphadenectomy in esophageal cancer after neoadjuvant therapy. A transthoracic lymphadenectomy allows for optimal staging and locoregional disease control, and an inadequate lymphadenectomy may lead to positive lymph nodes being missed.[160] Data regarding the lymph node status of individual lymph node stations would be of great importance before deciding to modify the extent of lymphadenectomy. The distribution of lymph node metastases is currently researched in a multinational observational cohort study with 58 participating centers (i.e, the TIGER study, NCT03222895).

The role of surgery beyond locally advanced disease

Since multimodality treatment for esophageal cancer is increasingly applied and can induce high degrees of tumor regression, even tumors that invade other adjacent structures such as aorta, vertebral body or trachea (T4b tumors) may be considered for resection in selected cases.[161] Furthermore, it has been reported feasible and beneficial in terms of survival to perform a radical resection combined with off-pump descending aorta replacement and adjuvant chemotherapy in 47 patients with a T4b esophageal tumor invading the aorta.[162] Also, there is evidence that patients with cT4b tumors can be safely treated with RAMIE

after long-course chemoradiotherapy and restaging with PET-CT.[161] A radical resection rate of 90% could be achieved in a case series of 10 patients.[161]

The selection of patients with oligometastases (<5 metastases) for surgery is of particular interest. The therapeutic approach to these patients is currently undergoing a shift towards a more aggressive treatment including surgical resection.[163] A radical surgical resection of the primary tumor and the metastases can be performed in patients who respond well to multimodal chemotherapy. The recently published results of the FLOT 3 study show that patients with limited metastatic disease after 4 cycles of neoadjuvant chemotherapy followed by routine surgical resection have a favorable survival compared to patients that received 8 cycles of chemotherapy and only a surgical intervention for a palliative indication.[164] Patient selection for surgical resection was based on a realistic chance for R0 resection of the primary tumor, and the possibility of at least a macroscopic complete resection of the metastatic lesions as evaluated by endoscopy and CT or MRI scans.[164] To identify patients that would benefit from such an aggressive treatment, response to systemic treatment and the 'test of time' (stable disease during follow-up) are currently the only useful markers.[165] Ongoing randomized studies mainly focus on oligometastatic disease in patients with GEJ and gastric adenocarcinoma. The ongoing German FLOT 5 study (NCT02578368) compares chemotherapy followed by surgery versus chemotherapy alone in patients with GEJ or gastric adenocarcinoma on overall survival. The German RENAISSANCE study[166] (NCT02578368) includes patients with limited metastatic disease, defined as either retroperitoneal lymph node metastases only, or a maximum of one organ site that is potentially resectable or locally controllable with or without retroperitoneal lymph nodes. All patients will receive 4 cycles of FLOT (combined with trastuzumab if HER-2-positive), and are randomized to receive additional chemotherapy cycles or surgical resection of primary tumor and metastases followed by adjuvant chemotherapy. Overall survival will be used as primary endpoint. Lastly, the GASTRIPEC study (NCT02158988) evaluates the value of intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to perioperative chemotherapy and gastrectomy for patients with GEJ and gastric cancer with synchronous peritoneal carcinomatosis.[167]

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Enhanced Recovery After Esophagectomy in the postoperative setting

After surgery, patients should first be able to mobilize as freely as possible to facilitate quick return to an acceptable activity level. To this end, the number of drains is preferably minimized and pain management should be effectively organized.[66] For gastrectomy for instance, routine placement of drains and nasogastric tubes is no longer recommended since their use has no proven benefit.[60] However, esophagectomy usually involves an

extensive thoracic procedure and temporary chest drainage remains to be considered necessary to prevent pulmonary compression by accumulation of air or fluid.[66] Although direct evidence is lacking for esophagectomy, literature on open pulmonary surgery suggests that the use of a single drain is safe and that drains can be removed when producing less than 200 milliliters per day.[66,168,169] However, due to the sparsity of literature specifically addressing chest drainage after esophagectomy, postoperative drainage protocols vary widely and more research is needed to achieve consensus.

Besides limiting the number of drains that potentially hamper mobilization, adequate pain management is essential to facilitate fast recovery.[170] Epidural analgesia is currently the gold standard after esophagectomy, as it was shown to be superior to systemic analgesia after open esophagectomy in terms of pain relief and pulmonary complications.[171,172] Nonetheless, this technique can suffer from several potential problems such as failed placements, catheter occlusions or dislocations, and epidural related complications (e.g., hypotension, nausea, abscess, hematoma).[173,174] With the rise of MIE, alternative techniques are increasingly investigated and applied[96,175] In a recent systematic review and meta-analysis, paravertebral analgesia was suggested to be a serious option as it may provide equal pain control while possibly causing less complications such as hypotension, nausea and urinary retention when compared to epidural analgesia.[175] However, well-designed prospective studies are warranted to provide more clarity on the optimal pain management modality.

Early resumption of oral intake is part of ERAS protocols to stimulate the return of bowel function. However, esophagectomy is somewhat unique due to the construction of a gastric conduit and a necessary vagotomy, which leads to delayed gastric emptying in 10-15% of patients.[176] Previous studies suggested that it may be safe to allow clear liquids from postoperative day 1,[177] but feeding protocols vary widely.[178,179] Currently, a randomized trial comparing early versus delayed start of oral intake after minimally invasive and hybrid esophagectomy is in its inclusion phase (i.e., the NUTRIENT II trial).[180] The results of this study are expected to provide more clarity regarding the role of early oral intake in the context of enhanced recovery after esophagectomy.

Conclusion and future directions

With the implementation and favorable results of neoadjuvant therapy, curation is possible for an increased number of esophageal cancer patients. However, adequate staging and thorough examination of the general condition are essential to select patients who are eligible for, and would benefit from, esophagectomy. Over the last decades, minimally invasive techniques are increasingly used and have shown promising results. However, not only the surgical procedure itself, but the entire perioperative care pathway should be

effectively organized in order to optimize surgical outcome. With this in mind, treatment of esophageal cancer with curative intent should be performed by a multidisciplinary team that is experienced in providing this type of care.

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Frequency of surgical resection after starting neoadjuvant chemoradiotherapy in patients with esophageal cancer: a population-based cohort study

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Abstract

Background
Neoadjuvant chemoradiotherapy (nCRT) for resectable esophageal cancer is accompanied by the risk of treatment-related toxicity. The aim of this population-based cohort study was to provide insight in patients who do not proceed to surgical resection after starting nCRT.

Methods
Patients who started nCRT for primary esophageal cancer diagnosed in 2015 and 2016 were selected from the nationwide population-based cancer registry. Outcome measurements included omission from surgical resection, reasons for omission of surgical resection, mortality during nCRT (≤90 days after ending nCRT) and 1-year overall survival. Multivariable logistic regression analyses were performed to identify predictive factors for omission of surgical resection.

Results
A total of 1521 patients were included, of whom 215 (14.1%) did not undergo surgical resection after starting nCRT. Age (OR: 1.04, 95% CI: 1.01-1.06), BMI (OR: 0.95, 95% CI: 0.90-0.99), WHO performance status (WHO 1: OR: 1.62, 95% CI: 1.16-2.62 and WHO 2: OR: 3.53, 95% CI: 1.68-7.41) and clinical N status (cN2: OR: 1.57, 95% CI: 1.04-2.37 and cN3: OR: 2.52, 95% CI: 1.14-5.55) were significantly associated with omission from surgery. The most frequently reported reasons for omission from surgery were disease progression (44.3%) and physical functioning (22.8%). During nCRT or within the subsequent waiting period to surgery, 38 patients (2.5%) deceased. One year overall survival of the patients who underwent nCRT followed by surgical resection was 94.9%, and 73.5% in the patients who did not undergo surgical resection following nCRT.

Conclusions
One in 7 patients who started nCRT for esophageal cancer do not proceed to surgical resection and have a decreased one year overall survival compared to patients who do proceed to surgical resection. Mortality during nCRT is considerable.

Introduction

Esophagectomy with lymphadenectomy remains the cornerstone of curative treatment for locally advanced esophageal cancer. Improved quality measures[1], such as centralization[2–5] and enhanced perioperative care,[6,7] have resulted in decreased morbidity and mortality rates following surgical resection. Neoadjuvant chemoradiotherapy (nCRT) has been increasingly recognized as an integral component of the curative treatment of esophageal cancer, improving overall survival compared to surgery alone.[8–11] Despite its prognostic benefits, nCRT is nevertheless not without the risk of treatment-associated toxicities. Several studies have focused on complications during neoadjuvant therapy and their effects on surgical morbidity and short- and long-term survival.[12–14] This is especially relevant when these toxic effects prevent patients from undergoing surgical resection. Well-known randomized controlled intervention trials report omission from surgical resection after starting nCRT in up to 15% of patients (1.8%[8] to 15.4%[11]) and mortality rates of <1% during nCRT (0%[11] to 0.6%[8]). As trial populations are carefully selected based on strict inclusion criteria – e.g. patients with limited comorbidities –, the representativeness of these results for the general cancer population might be compromised[15].

Therefore, the aim of this population-based cohort study was to describe the patients with esophageal cancer who do not proceed to surgical resection after starting nCRT, as well as to identify potential predictive factors for unplanned omission from surgical resection and to describe the reasons for unplanned omission from surgical resection. Better understanding of the factors placing patients at higher risk of not proceeding to surgical resection may ultimately improve clinical decision making. Moreover, the mortality rate during nCRT, or in the subsequent waiting period to surgery for esophageal cancer was described.

10

Material and methods

Study design
This population-based observational cohort study included data from the Netherlands Cancer Registry (NCR). The NCR registers cases based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses and radiotherapy institutions. The NCR stores data on patient, tumor and treatment characteristics. Data is routinely extracted from hospital records by trained data managers. Information on a patient's vital status is updated through an annual linkage with the municipal personal records database, in which all deceased and emigrated persons in the Netherlands are registered.

This study was approved by the Privacy Review Board of the NCR. According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands.

Study population

For the purpose of this study, all patients with esophageal cancer in the Netherlands who started nCRT in 2015 and 2016 were selected. Patients with distant metastases before the start of nCRT (M1) and a histologic tumor type other than adenocarcinoma or squamous cell carcinoma were excluded. Data on patient and treatment-related characteristics, histopathological characteristics, and follow-up were extracted from the NCR. As exact chemotherapy and radiotherapy regimens, as well as initial treatment plans for individual patients have been registered by the NCR from 2015 onwards, patients could specifically be selected that started nCRT according to the CROSS regimen (carboplatin targeted at an area under the curve (AUC) of 2 mg/ml/min and paclitaxel at a dose of 50mg/m^2, weekly during 5 weeks, and concurrent radiotherapy with a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy[8]).

Patients were diagnosed according to the Dutch national guidelines for patients with esophageal cancer.[16] The diagnostic work-up consisted of at least endoscopy with tumor biopsy and computed tomography (CT) with or without positron emission tomography (PET). Patients were staged according to the 7th edition of the Union for International Cancer Control (UICC) TNM staging system.[17]

Surgery was defined as actual surgical resection, by means of a transhiatal or transthoracic esophagectomy, either open or minimally invasive, but always combined with a lymphadenectomy. The choice of technique was at the discretion of the treating surgeon.

CROSS eligibility criteria were defined as age 18 - 75 years, a WHO performance status of ≤ 2, clinical T status ≤ T3, tumor length ≤8 cm and no history of other cancer. All patients in this cohort were M0. No data was available in the NCR to account for the remaining eligibility criteria of the CROSS trial (i.e. lost 10% or less of body weight, no previous radiotherapy or chemotherapy, adequate hematologic, renal, hepatic, and pulmonary function).[8]

Outcome measures

Whether or not surgical resection was performed was routinely registered by the NCR. Reasons for omission from surgical resection in patients who started nCRT were registered based on standardized categories for patients diagnosed in 2015 only.

Mortality during nCRT was defined as all-cause mortality during nCRT, or within the subsequent waiting time to surgery (≤90 days after the end date of nCRT), and always before the intended surgical resection.

Follow-up time was measured from start of nCRT, and was completed for all patients until January 1st, 2018. Survival time was defined as time from diagnosis to death or until January 1st, 2018 for patients who were still alive.

Statistical analyses

Patient and treatment-related characteristics were described as counts with percentages or mean (± standard deviation [SD]). The number of patients who did not undergo surgical resection after starting nCRT and the corresponding reasons for not undergoing surgical resection (only of the patients diagnosed in 2015), as well as the mortality during nCRT or the subsequent waiting period was described.

To be able to identify potential predictive factors for omission from surgical resection after starting nCRT, missing values were imputed using multiple imputation (Multivariate Imputation by Chained Equations, 30 imputed datasets with a maximum number of 20 iterations for each imputation).[18,19] Variables to be entered in the multivariable logistic regression model with omission from surgery as outcome were based on clinical reasoning and literature review, and consisted of age, sex, body mass index (BMI), performance status, number of comorbidity categories, clinical T status, clinical N status, tumor histology and whether or not patients met the eligibility criteria of the CROSS trial. No further predictor selection was performed. Model coefficients were pooled using Rubin's rules.

Survival curves were obtained using the Kaplan–Meier method.

Statistical analyses were performed using R open-source software ('mice' and 'glm' packages, version 3.5.1) and GraphPad Prism version 7.04 (La Jolla, California, USA). For the multivariable logistic regression model, the p-value was deemed to be less than or equal to 0.05, and the effect was said to be significant, if the confidence interval failed to include 1.

Results

Study population

The study cohort included 1521 patients who started nCRT for potentially resectable esophageal cancer in the Netherlands in 2015 and 2016. A complete overview of patient and treatment-related characteristics is presented in Table 1. The majority of patients was male (78.3%, 1191/1521) with a mean age of 65.1 years (SD ± 8.8) and a WHO performance status at diagnosis of 0 (52.5%, 798/1521) or 1 (30.4%, 462/1521). Most tumors were distal esophageal adenocarcinomas with clinical T2-3 status and accompanied by at least 1 lymph node metastasis (clinical N1-3).

A total of 457 patients (30.0%) exceeded the original eligibility criteria of the CROSS trial based on one or a combination of the following characteristics: age ≥ 75 years (n=211), cT4

Table 1. Baseline characteristics of patients who started neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer in the Netherlands in 2015 and 2016

Characteristics	All		Omission from surgical resection		Deceased during nCRT*	
	n = 1521	(%)	n = 215	(%)	n = 38	(%)
Age, years (mean ± SD)	65.1 ± 8.8		67.6 ± 9.4		68.0 ± 8.3	
Sex						
Male	1191	78.3%	169	78.6%	34	89.5%
Female	330	21.7%	46	21.4%	4	10.5%
BMI, kg/m² (mean ± SD)	26.1 ± 4.3		25.1 ± 4.2		25.9 ± 4.7	
Unknown	483	31.8%	126	58.6%	15	39.5%
WHO performance status						
0	798	52.5%	86	40.0%	12	31.6%
1	462	30.4%	81	37.7%	15	39.5%
2	38	2.5%	13	6.0%	5	13.2%
3	1	0.1%	1	0.5%	0	0.0%
Unknown	222	14.6%	34	15.8%	6	15.8%
Comorbidity categories [†]						
None	419	27.5%	45	20.9%	4	10.5%
One category	448	29.5%	54	25.1%	7	18.4%
Two or more categories	516	33.9%	94	43.7%	22	57.9%
Unknown	138	9.1%	22	10.2%	5	13.2%
Specific comorbidities						
Hypertension	497	32.7%	78	36.3%	17	44.7%
Cardiovascular comorbidities (other than hypertension)	398	26.2%	76	35.3%	19	50.0%
Diabetes mellitus	204	13.4%	40	18.6%	8	21.1%
Pulmonary comorbidities	199	13.1%	35	16.3%	7	18.4%
History of cancer	169	11.1%	24	11.2%	5	13.2%
Gastrointestinal comorbidities	84	5.5%	14	6.5%	4	10.5%
Renal	22	1.4%	9	4.2%	1	2.6%
Liver	17	1.1%	1	0.5%	0	0.0%
Tumor location						
Proximal esophagus	14	0.9%	6	2.8%	2	5.6%
Middle esophagus	176	11.6%	29	13.5%	3	7.9%
Distal esophagus	1162	76.4%	146	67.9%	25	65.8%
Esophagus not otherwise specified	52	3.4%	13	6.0%	3	7.9%
Cardia	117	7.7%	21	9.8%	5	13.2%
Histology						
Adenocarcinoma	1202	79.0%	159	74.0%	30	78.9%
Squamous cell carcinoma	319	21.0%	56	26.0%	8	21.1%
Tumor differentiation						
Well	51	3.4%	8	3.7%	1	2.6%
Moderate	628	41.3%	72	33.5%	8	21.1%
Poor	533	35.0%	72	33.5%	13	34.2%
Unknown	309	20.3%	63	29.3%	16	42.1%

Table 1. Continued

Characteristics	All		Omission from surgical resection		Deceased during nCRT*	
	n = 1521	(%)	n = 215	(%)	n = 38	(%)
Clinical T status ‡						
T1	22	1.4%	3	1.4%	0	0.0%
T2	458	30.1%	52	24.2%	11	28.9%
T3	981	64.5%	145	67.4%	25	65.8%
T4	22	1.4%	6	2.8%	1	2.6%
Unknown	38	2.5%	9	4.2%	1	2.6%
Clinical N status ‡						
N0	602	39.6%	73	34.0%	7	18.4%
N1	575	37.8%	76	35.3%	16	42.1%
N2	282	18.5%	52	24.2%	12	31.6%
N3	40	2.6%	10	4.7%	3	7.9%
Unknown	22	1.4%	4	1.9%	0	0.0%
Year of diagnosis						
2015	732	48.1%	79	36.7%	14	36.8%
2016	789	51.9%	136	63.3%	24	63.2%
Exceeded original CROSS eligibility criteria §	457	30.0%	82	38.1%	13	34.2%

BMI body mass index at diagnosis; *nCRT* neoadjuvant chemoradiotherapy; *WHO* World Health Organization
* Please note: the patients who deceased during neoadjuvant chemoradiotherapy are also included in the patients who did not undergo surgical resection.
† Closely related comorbidities were considered as one category.
‡ Clinical T status and N status are based on UICC TNM 7th edition.
§ CROSS eligibility criteria were defined as age 18-74 years, clinical T status ≤ T3, no history of other cancer, tumor length ≤8 cm and WHO ≤ 2 (Note: all patients in this cohort were cM0).

status (n=22), tumor length >8 cm (n=125), history of other cancer (n=169) and WHO performance status of > 2 (n=1).

Patients in the cohort who underwent a surgical resection of the primary tumor, underwent this resection at a median of 62 days after the last day of nCRT (interquartile range 52-77 days).

Omission from surgical resection

A total of 215 patients (14.1%) did not undergo surgical resection after starting nCRT. These patients had a mean age of 67.6 (SD ± 9.4) years and mostly a moderate to poorly differentiated adenocarcinoma of the distal esophagus. Furthermore, 38.1% (82/215) of these patients exceeded the original eligibility criteria of the CROSS trial.

Multivariable logistic regression analysis with omission from surgical resection as outcome identified age (pooled odds ratio [OR]: 1.04, 95% CI: 1.01-1.06), BMI (pooled OR: 0.95,

95% CI: 0.90-0.99), WHO performance status (WHO 1: pooled OR: 1.62, 95% CI: 1.16-2.62 and WHO 2: pooled OR: 3.53, 95% CI: 1.68-7.41) and clinical N2 or N3 status (pooled OR: 1.57, 95% CI: 1.04-2.37 and pooled OR: 2.52, 95% CI: 1.14-5.55, respectively) to be significantly associated with omission from surgical resection (Table 2). Exceeding the original eligibility criteria of the CROSS trial was not independently associated with a higher odds for omission of surgery (pooled OR: 0.99, 95% CI: 0.70-1.40).

Table 2. Multivariable logistic regression analyses with omission from surgery as outcome variable

Predictors	Complete case analysis (n=833)		Multiple imputation (30 datasets)	
	Odds ratio	95% CI	Odds ratio	95% CI
Age, years	1.02	0.99 – 1.05	1.04	1.01 – 1.06
Sex				
Male	reference		reference	
Female	1.07	0.60 – 1.86	0.81	0.55 – 1.20
BMI, kg/m²	0.95	0.90 – 1.00	0.95	0.90 – 0.99
WHO performance status				
0	reference		reference	
1	1.83	1.15 – 2.89	1.62	1.16 – 2.62
2	3.54	1.05 – 10.46	3.53	1.68 – 7.41
Comorbidity categories †				
None	reference		reference	
One category	0.73	0.40 – 1.31	0.91	0.59 – 1.41
Two or more categories	0.88	0.50 – 1.57	1.39	0.90 – 2.16
Histology				
Adenocarcinoma	reference		reference	
Squamous cell carcinoma	1.38	0.79 – 2.37	1.28	0.87 – 1.87
Clinical T status ‡				
T1-T2	reference		reference	
T3-T4	1.50	0.87 – 2.68	1.21	0.85 – 1.72
Clinical N status ‡				
N0	reference		reference	
N1	1.63	0.94 – 2.87	1.07	0.75 – 1.54
N2	2.92	1.60 – 5.40	1.57	1.04 – 2.37
N3	4.85	1.56 – 13.68	2.52	1.14 – 5.55
Exceeded original CROSS eligibility criteria §	1.17	0.71 – 1.91	0.99	0.70 – 1.40

BMI body mass index at diagnosis; *WHO* World Health Organization
† Closely related comorbidities were considered as one category.
‡ Clinical T status and N status are based on UICC TNM 7th edition.
§ CROSS eligibility criteria were defined as age 18-74 years, cT status ≤ T3, no history of other cancer, tumor length ≤8 cm and WHO ≤ 2(Note: all patients in this cohort were cM0).
Note. All variables included in this table were used for multiple imputation of the missing variables, as well as tumor location, tumor differentiation and the outcome. One patient with a WHO performance of 3 was excluded from the complete case analysis as well as the multiple imputation analysis. Bold values reflect significant odds ratio's. The intercept of the model of the complete case analysis was -3.28 and for the model after multiple imputation -3.46.

The most frequently reported reasons for not proceeding to surgical resection in 2015 were disease progression (43.0%, n=34), physical functioning (22.8%, n=18) and patient preference (16.5%, n=13) (Table 3).

Mortality during neoadjuvant therapy

A total of 38 patients (2.5%) deceased during nCRT or the subsequent waiting period to surgery. The majority of the deceased patients were male (89.5%), with a mean age of 68.0 (SD ± 8.3) years. Most deceased patients had a WHO performance status of 1 (39.5%, 15/38), comorbidities in ≥2 categories (57.9%, 22/38), of which cardiovascular comorbidities and hypertension were the most frequently present (50.0% [19/38] and 44.7% [17/38], respectively). Furthermore, 81.6% (31/38) of patients had at least 1 lymph node metastasis at clinical staging (clinical N1-3). Among these deceased patients, 34.2% (n=13) exceeded the original eligibility criteria of the CROSS trial. A detailed description of these patient demographics is included in Table 1. The patients who deceased during nCRT are also included in the patients who did not undergo surgical resection.

Table 3. Reasons for omission from surgery in patients who started neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer in 2015

Reasons	n	(%)
All patients who started nCRT but did not proceed to surgery in 2015	79	100%
Disease progression	34	43.0%
Impaired physical functioning	18	22.8%
Patient preference	13	16.5%
Comorbidities	2	2.5%
Complications or toxicity of previous therapy	3	3.8%
Low tumor load	1	1.3%
Other/unknown	8	10.1%
Subgroup of patients who did not proceed to surgery and deceased during nCRT or subsequent waiting period to surgery in 2015	15	100%
Disease progression	4	26.7%
Impaired physical functioning	3	20.0%
Patient preference	1	6.7%
Comorbidities	1	6.7%
Complications or toxicity of previous therapy	2	13.3%
Low tumor load	0	0.0%
Other/unknown	4	26.7%

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Survival

Kaplan-Meier survival curves for 1-year overall survival of all patients with esophageal cancer that started nCRT per treatment group (i.e. nCRT followed by surgery and nCRT without surgery) are depicted in Figure 1. No patients were censored, as follow-up time included at least 365 days from start of nCRT for all patients. One-year overall survival of the patients who underwent nCRT followed by surgical resection was 94.9%. One-year overall survival of the patients who did not undergo surgical resection was 73.5%.

1-Year Overall Survival
All patients who started nCRT
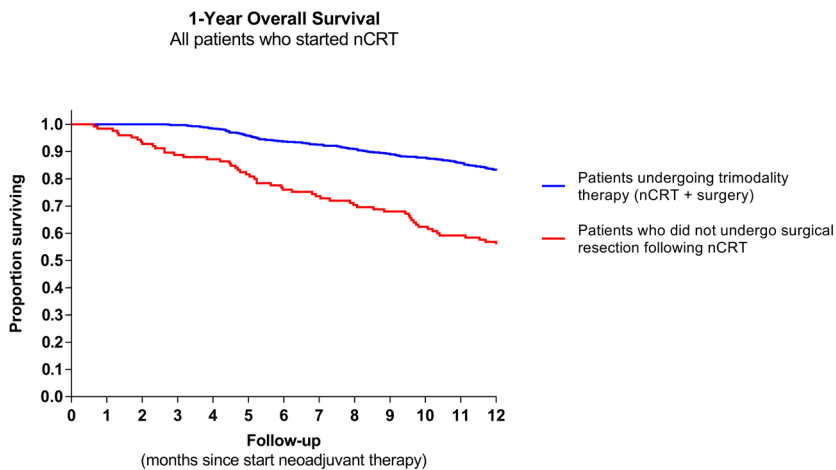
Number at risk					
nCRT + surgery	697	696	654	622	581
nCRT without surgery	125	112	96	86	71

Figure 1. Kaplan-Meier estimates of 1-year overall survival for patients with esophageal cancer that started neoadjuvant chemoradiotherapy (nCRT) in the Netherlands in 2015 and 2016. Please note that the categorization of patients by treatment, results in immortal time bias from the start of neoadjuvant therapy until the date of surgery for patients who underwent nCRT followed by surgery (blue curve).

Discussion

This population-based observational cohort study aimed to gain insight in unplanned omission from surgical resection after starting nCRT for esophageal cancer, arising from patient preference and disease progression as reasons for not proceeding to surgical resection, as well as mortality during nCRT. It demonstrated that 1 in 7 (14.1%) patients did not undergo the planned surgical resection and 1 in 40 (2.5%) of patients who started nCRT for esophageal cancer deceased during nCRT or in the subsequent waiting period to surgery.

Surgery following nCRT in patients with locally advanced esophageal cancer is associated with significantly improved survival compared to chemoradiotherapy alone (i.e. definitive CRT), especially for esophageal adenocarcinoma.[20,21] Furthermore, salvage surgery appears to be associated with poorer short-term outcomes in patients with persistent or recurrent disease after definitive CRT, when compared to planned esophagectomy following nCRT.[22] As such, curative treatment should aim to include surgical resection and patients and multidisciplinary tumor boards should be made aware of these differences in outcomes.[22] However, in our cohort, 14.1% of patients who were deemed eligible for nCRT followed by esophagectomy did not undergo surgical resection, which is higher than the percentage reported in the randomized controlled CROSS trial (7.6%). The main reason for not undergoing surgical resection in the cohort from 2015 was disease progression. Disease progression, including systemic interval metastases, was reported as reason for not undergoing surgical resection in 4.8% of the entire cohort from 2015 (35/732). Contrarily, studies reporting on the value of a standard restaging PET-CT after nCRT in detecting interval metastases observed interval metastases in 8% of cases.[23,24] The discrepancy between these results and the results obtained in the present study is most likely to be explained by the fact that a restaging PET-CT was not routinely performed in the Netherlands in 2015. As such, interval metastases could have remained unnoticed and the 4.8% disease progression found in our study is most likely under-reported. Disease progression as reason for omission from surgical resection might furthermore be reflected in the finding that clinical N2 or N3 status was significantly associated with a higher odds of omission of surgical resection, as it has been described that positive N status at diagnosis increases the probability of developing interval metastases.[24]

Physical functioning, the reduction thereof reported as a reason for not undergoing surgical resection in 22.8% of patients who did not undergo surgical resection in 2015, could be increased by structured counseling by a multidisciplinary team of physical therapists and dieticians.[25] The time between diagnosis and nCRT, as well as the interval between nCRT and surgical resection, is highly suitable for interventions to stimulate a patients physical functioning. This might subsequently allow these patients to undergo surgical resection after all.

Patient preference was reported as the reason for not undergoing surgical resection in 16.5% of these patients, which underlines the importance of counseling and shared decision making. Besides survival, quality of life is highly relevant to patients in treatment decision-making.[26] As esophagectomy has a lasting impact on quality of life, this might be another reason for patients to opt for not undergoing surgical resection.[27,28] A shared decision-making tool, which aims to transparently discuss both the benefits and drawbacks from all treatment strategies including survival and quality of life between the patient and their physician, might further aid informed shared decision-making.

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This patient preference might furthermore be driven by increasing attention for patients with a clinical complete response after nCRT, in whom an active surveillance approach might be feasible.[29] However, to date survival is significantly better for patients with a clinical complete response to nCRT who underwent surgery compared to active surveillance.[21,30] This is most likely influenced by the lack of reliable diagnostic tests to accurately select patients with a pathological complete response. As such, it is felt that an accurate model should first be developed, before pursuing an active surveillance approach in clinical practice. Given the patient selection criteria that are employed in randomized controlled trials, the applicability of nCRT to all patients with esophageal cancer might be questionable.[12] The results of the present study show that the eligibility criteria for nCRT in clinical practice have been extended in one third of the patients, which might have led to a higher mortality rate during nCRT or in the subsequent waiting period to surgery than in the randomized controlled CROSS trial (2.5% versus 0.6%, respectively). Previous single center studies however have demonstrated that extension of the CROSS eligibility criteria for nCRT did not affect nCRT associated toxicity or survival.[31,32] The difference between the single center studies and the current population-based study might be explained by hospital variation, as hospital variation is a known important factor to influence treatment for esophageal cancer.[33] As such, hospital variation might also influence the support vulnerable patients who undergo nCRT receive. Exceeding the original eligibility criteria of the CROSS trial was not significantly associated with unplanned omission from surgical resection in the current cohort, even though the patients who did not undergo surgical resection following nCRT was double that of the CROSS trial. This difference might not only explained by the selection bias caused by employing strict inclusion criteria, but also by the selection bias of patients who are willing to participate in a randomized controlled trial. Furthermore, no data was available in the registry to account for weight loss, previous radiotherapy or chemotherapy as well as hematologic, renal, hepatic, and pulmonary function, which are the remaining eligibility criteria of the CROSS trial. These patient-related factors might also have contributed to more patients who did not proceed to surgical resection in the current study, but could not be accounted for.

Our results show age, BMI at diagnosis and performance status to be associated with unplanned omission from surgery. It is important to realize that our descriptive study merely describes current clinical practice. Hence, no causal conclusions can be drawn whether older patients or patients with an impaired performance status should undergo nCRT before esophagectomy based on the current data, nor based on the (conflicting) results reported by previous literature on this matter.[34–39] Overall, advanced age should not be considered as a strict contraindication to either nCRT or esophagectomy. Whether or not nCRT should function as selection mechanism for patients who are eligible for surgery, or patients should be selected for nCRT remains unresolved. Nevertheless, even though factors like age and performance status are not modifiable, our results could aid physicians

in the identification of patients who might benefit from increased counseling in the preoperative trajectory, i.e. patients with higher age, lower BMI and impaired performance status. These patients could be offered supervised prehabilitation for surgery, a preoperative geriatric assessment to obtain a holistic view of the patient or more frequent follow-up visits with their own oncologist or surgeon to motivate them and their caregivers for surgery. Insights into these factors will help treating clinicians and their patients predict the balance of harms and benefit and may ultimately improve clinical decision making.

Baseline differences between patient groups are furthermore likely to influence the observed differences in the 1-year overall survival curves for the different treatment groups (as depicted in Figure 1). Since the study data is obtained from routine clinical practice, confounding by indication as form of selection bias for these treatment strategies will likely influence the observed results. Therefore, these results warrant careful interpretation and no statistical analyses were performed for this comparison.

The population-based design with virtually complete inclusion of all eligible patients in the Netherlands is a significant strength of the study, along with the fact that we had detailed information on the nCRT regimen and all patients underwent the same regimen. It should be noted that there are also limitations associated with population-based observational studies such as this, for instance the lack of knowledge on the cause of death and hospital information.

In summary, mortality during nCRT for esophageal cancer is considerable. Furthermore, 1 in 7 patients who started nCRT eventually does not proceed to surgical resection. These patients have a lower overall survival compared to the patients who undergo nCRT followed by surgical resection. This could be a starting point for further research, which should aim to investigate whether this patient group can be selected prior to treatment, and whether patient-individualized treatment, centralization of oncological care and counseling will result in a larger proportion of patients who will undergo surgery.

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

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Joint first authorship.

Abstract

Background
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.

11

Patients and 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.
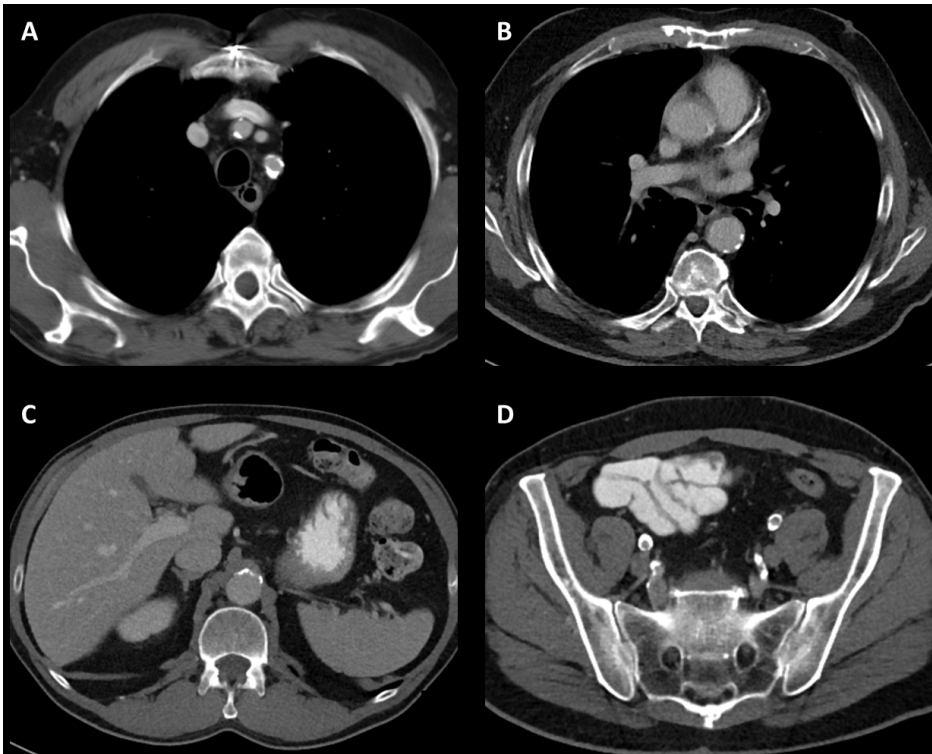
Figure 1. Examples of preoperative CT images of arterial calcification in patients with esophageal cancer.
A: Calcification of the brachiocephalic and left subclavian artery, resulting in a score of 2 for calcification of the supra-aortic arteries.
B: Calcification of a large segment of the left anterior 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.

11

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

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.

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.

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

11
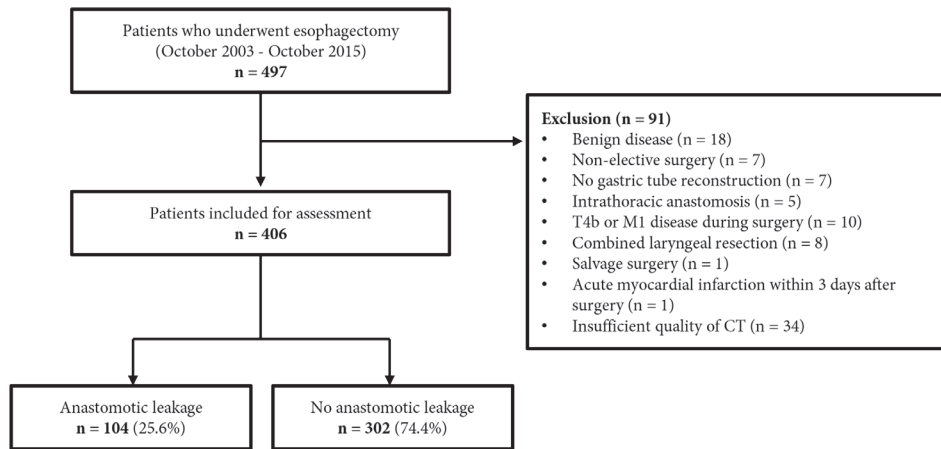
Figure 2. Flowchart of study design

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.

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

Characteristic	Anastomotic leakage	No anastomotic leakage	p-value
	n = 104 (25.6%)	n = 302 (74.4%)	
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/m²)	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
Year of surgery			.280
2003-2008	25 (24.0)	56 (18.5)	
2009-2010	15 (14.4)	71 (23.5)	
2011-2012	26 (25.0)	71 (23.5)	
2013-2014	28 (26.9)	69 (22.8)	
2015	10 (9.6)	35 (11.6)	

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)

11

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 n=104 (25.6%)	No anastomotic leakage n = 302 (74.4%)	Unadjusted odds-ratio (95% CI)	p-value	Adjusted odds-ratio* (95% CI)	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)				

CI confidence interval; *NA* not available.

Values in the third and fourth column represent numbers of patients, with row-based percentages in parentheses.

* Adjusted for age at diagnosis, BMI, history of cardiovascular disease, COPD, diabetes mellitus and smoking.

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 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.

11

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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11

Safety and feasibility of minimally invasive surgical interventions for esophageal and gastric cancer in the acute setting: a nationwide cohort study

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Abstract

Background
Minimally invasive esophagectomy and gastrectomy are increasingly performed and might be superior to their open equivalents in an elective setting. The aim of this study was to evaluate whether minimally invasive approaches can be safely applied in the acute setting as well.

Methods
All patients who underwent an acute surgical intervention for primary esophageal or gastric cancer between 2011-2017 were identified from the nationwide database of the Dutch Upper GI Cancer Audit (DUCA). Conversion rates, postoperative complications, reinterventions, postoperative mortality, hospital stay and oncological outcomes (radical resection rates and median lymph node yield) were evaluated.

Results
Between 2011-2017, surgery for esophagogastric cancer was performed in an acute setting in 2% (190/8861) in The Netherlands. A total of 14 acute resections for esophageal cancer were performed, which included 7 minimally invasive esophagectomies and 7 open esophagectomies. As these numbers were very low, no comparison between minimally invasive and open esophagectomies was made.
A total of 122 acute resections for gastric cancer were performed, which included 39 minimally invasive gastrectomies and 83 open gastrectomies. Conversion occurred in 9 patients (23%). Minimally invasive gastrectomy was at least comparable to open gastrectomy regarding postoperative complications (36% versus 51%), median hospital stay (9 days [IQR: 7-16 days] versus 11 days [IQR: 7-17 days]), readmissions (8% versus 11%) and oncological outcomes (radical resection rate: 87% versus 66%, median lymph node yield: 21 [IQR: 15-32] versus 16 [IQR: 11-24]) .

Conclusions
Minimally invasive surgery for gastric cancer is safe and feasible in the acute setting, with at least comparable postoperative clinical and short-term oncological outcomes compared to open surgery but a relatively high conversion rate.

Introduction

Minimally invasive surgical techniques are increasingly being applied in the surgical treatment of esophageal and gastric cancer.[1,2] Evidence from randomized controlled trials and nationwide studies suggests that these techniques might provide benefits over the traditional open approaches, especially regarding short-term outcomes in terms of postoperative morbidity and length of hospital stay.[3–12] In contrast, higher reintervention rates were observed after minimally invasive esophagectomies in population-based studies.[5–8] As the aforementioned studies only included patients who underwent an elective surgical resection, the generalizability of these results to the acute setting might be limited. Acute surgery for esophageal and gastric cancer is relatively rare and is usually only performed in case tumors are actively bleeding or have perforated. These cases are different from the usual elective patient population and might therefore be more difficult to treat with minimally invasive surgical techniques. More research is warranted to investigate the role of minimally invasive surgical techniques for patients with esophageal and gastric cancer who have an acute indication for a resection. Therefore, the aim of this nationwide cohort study was to describe the postoperative outcomes of minimally invasive as compared to open acute surgery for esophageal and gastric cancer.

Methods

Study design
This nationwide observational cohort study was conducted with data from the Dutch Upper GI Cancer Audit (DUCA), a nationwide registration of all patients undergoing surgery for esophageal and gastric cancer since 2011.[13] Registration of cases in the DUCA is mandatory for each hospital and includes patient characteristics, treatment details including the timing of surgery, postoperative outcomes (until 30 days after surgery), and pathological outcomes. The scientific committee of the DICA and DUCA approved this study. No ethical approval or informed consent was required under Dutch law.

Study population and treatment
All patients who underwent acute surgery with the intention to perform an esophagectomy or gastrectomy for cancer between 2011-2017 were selected from the DUCA registry. Patients were diagnosed according to the Dutch national guidelines for diagnosis, treatment, follow up, and guidance of patients for patients with esophageal and gastric cancer.[14,15] Acute surgical interventions were either defined as emergent (i.e. surgery scheduled <12 hours after presentation with an acute indication) or urgent (surgery scheduled >12 hours

– but not electively – after presentation with an acute indication). Both were included in the current study. Exclusion criteria were prophylactic surgical indications (i.e. no proven malignancy), insufficient data regarding the tumor or surgical approach, and surgery for cancer recurrence.

Outcome measures

The outcome measures included the rates of conversion to an open procedure, postoperative complications, reinterventions, postoperative mortality (i.e. mortality during initial hospital admission or within 30 days after surgery), length of postoperative stay on the Intensive Care Unit (ICU) and in hospital, as well as readmissions (<30 days after discharge). Complications were defined according to standards of the DUCA, and included pulmonary complications (clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema and/or acute respiratory distress syndrome), anastomotic leakage (either by clinical or radiological diagnosis), cardiac complications (supraventricular and ventricular arrhythmia, myocardial infarction and/or heart failure), thromboembolic complications (pulmonary embolism, deep venous thrombosis, stroke and/or thrombophlebitis), neurologic complications (recurrent laryngeal nerve injury and/or acute delirium), urologic complications (urinary tract infection, urinary retention and/or renal insufficiency), intra-abdominal abscess, chyle leakage, fascia dehiscence and wound infections. Furthermore, oncological outcomes in terms of radicality and total lymph node yield were analyzed. A radical resection (i.e. R0) was defined as the absence of tumor cells within the resection margins of the resection specimen.

Statistical analyses

Patient and treatment characteristics were described as counts with percentages, mean (± standard deviation [SD]) or median (interquartile range [IQR]). The postoperative outcomes were separately described for patients who underwent minimally invasive surgery and open group. No tests for statistical significance of differences between groups were performed because of inability to adequately correct for confounding bias due to small group sizes. Statistical analyses were performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA).

Results

Study population

Between 2011-2017, a total of 8861 patients who underwent surgery for esophageal or gastric cancer in the Netherlands were registered in the DUCA. Surgery was performed in
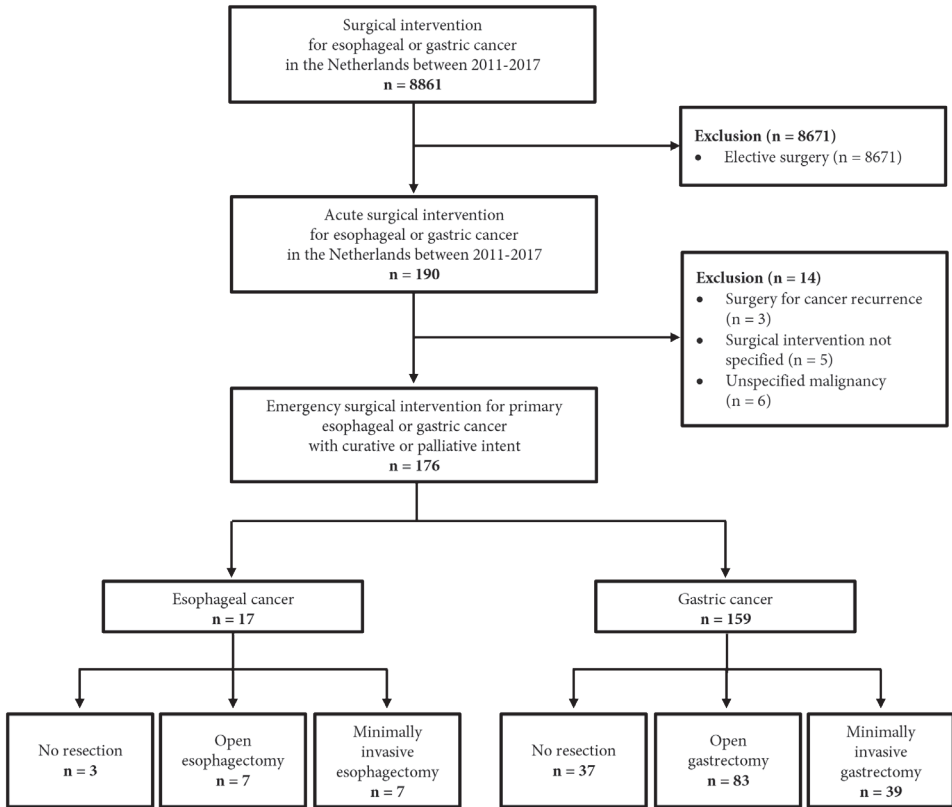
Figure 1. Study flowchart

an acute setting in 190 out of these 8861 patients (2%). Patients who underwent an unspecified surgical intervention (n=5), a surgical procedure for cancer recurrence (n=3), or a surgical procedure for an unspecified malignancy (n=6) were excluded. Hence, a total of 176 patients were included, of whom 17 patients with esophageal cancer and 159 patients with gastric cancer (Figure 1).

Acute surgical interventions for esophageal cancer

Acute surgical interventions for esophageal cancer were performed in 17 patients and were with curative intent in all of these patients. The median number of days between the diagnostic biopsy and surgery was 70 days (IQR 46 – 121 days). In 2 patients (12%), no histologic diagnosis was present prior to surgery. The reason for surgery was a perforation in 7 patients (41%), bleeding in 5 patients (29%) and other (not specified) in the remaining 5 cases (29%).

Table 1. Baseline characteristics of patients who underwent an acute surgical intervention for esophageal cancer in the Netherlands between 2011 and 2017.

Characteristics	All	
	n = 17	**%**
Patiënt-related characteristics		
Age, years (mean ± SD)	64 ± 11	
Sex		
Male	15	88%
Female	2	12%
BMI, kg/m² (mean ± SD)	26 ± 5	
ASA classification		
I	2	12%
II	7	41%
III	7	41%
IV	1	6%
Comorbidities		
Cardiac	2	12%
Vascular	8	47%
Diabetes	5	29%
Pulmonary	3	18%
Previous abdominal or thoracic surgery	7	41%
Tumor location		
Middle esophagus	1	6%
Distal esophagus	9	53%
Gastro-esophageal junction	5	29%
Unknown	2	12%
Histology		
Adenocarcinoma	15	88%
Squamous cell carcinoma	1	6%
Other	1	6%
cT status*		
T1	3	18%
T2	2	12%
T3	5	29%
T4	5	29%
Tx	2	12%
cN status*		
N0	6	35%
N+	8	47%
Nx	3	18%
cM status*		
M0	13	76%
M1	2	12%
Mx	2	12%

Table 1. Continued

Characteristics	All	
	n = 17	%
Treatment-related characteristics		
Neoadjuvant therapy[†]		
None	10	59%
Chemoradiotherapy	4	24%
Chemotherapy	2	12%
Radiotherapy	1	6%
Setting		
Emergent (<12 hours)	10	59%
Urgent (>12 hours)	8	41%
Reason for emergency surgery		
Bleeding	5	29%
Perforation	7	41%
Other/unknown	5	29%
Surgical approach		
Minimally invasive	9	53%
Open	8	47%
Surgical procedure		
Transhiatal esophagectomy	9	53%
Transthoracic esophagectomy	5	29%
Diagnostic thoracotomy	1	6%
Diagnostic laparoscopy	2	12%
Reconstruction		
Gastric conduit reconstruction	12	71%
No reconstruction	4	24%
Unknown	1	6%
Location of anastomosis		
Cervical	10	59%
Intrathoracic	2	12%
Not applicable	5	29%
Lymph node dissection	13	76%
Year of surgery		
2011 – 2013	9	53%
2014 – 2017	8	47%

ASA American Society of Anesthesiologists*; BMI* body mass index at diagnosis; *SD* standard deviation
Note. Data are numbers of patients with column-based percentages in parentheses, unless otherwise stated.
* Clinical T status and N status are based on AJCC TNM 7th edition.
[†] The standard regimen for neoadjuvant treatment for esophageal cancer patients in the Netherlands consists of carboplatin and paclitaxel, weekly during 5 weeks, and concurrent radiotherapy with a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy. For gastro-esophageal junction or gastric adenocarcinoma, peri-operative treatment generally consists of chemotherapy regimens similar to the MAGIC-trial (epirubicin, cisplatin and capecitabine).

12

Table 2. Short-term outcomes for patients who underwent an acute esophagectomy for esophageal cancer in the Netherlands between 2011 and 2017.

	Total	
	n = 14	%
Peroperative outcomes		
Conversion*	1	7%
Postoperative complications		
All	7	50%
Pulmonary†	6	43%
Anastomotic leakage‡	4	29%
Cardiac §	1	7%
Chyle leakage	0	0%
Reinterventions	1**	7%
Recovery		
ICU duration (median, IQR)	3	(1-6)
Length of stay (median, IQR)	13	(11- 26)
Postoperative mortality ⁋	1	7%
Readmission to hospital #	0	0%
Pathological outcomes		
Radicality		
R0	9	64%
R1	5	36%
Lymph node yield (median, IQR)	21	(12-26)
Positive lymph nodes harvested (median, IQR)	3	(1-10)

IQR interquartile range, *NA* not applicable
Note. There were no missing values for the variables described in this table.
* Conversion >30 minutes after start of surgery because of peroperative bleeding.
† Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome.
‡ Any clinically or radiologically proven anastomotic leakage.
§ Supraventricular and ventricular arrhythmia, myocardial infarction and/or heart failure.
⁋ Death during initial hospital admission or within 30 days after surgery.
Readmission to hospital within 30 days after initial discharge.
** Re-operation for anastomotic leakage.

Esophagectomy was performed in 14 out of these 17 patients (82%); by a minimally invasive transhiatal approach in 4 patients, an open transhiatal approach in 5 patients, a minimally invasive transthoracic approach in 3 patients, and an open transthoracic approach in 2 patients. The remaining 3 patients (18%) underwent a surgical procedure without resection, which involved a diagnostic laparoscopy in 2 patients and a diagnostic thoracotomy in 1 patient. A complete overview of patient and treatment characteristics of the esophageal cancer patients is presented in Table 1.

Perioperative and oncological outcomes of the 14 patients who underwent esophagectomy are shown in Table 2. The outcomes were not reported for minimally invasive esophagectomy and open esophagectomy separately, as the number of patients for both groups was only 7. Postoperative complications occurred in 50% (7/14). Pulmonary complications were most common (43%, 6/14), followed by anastomotic leakage (29%, 4/14). The median length of hospital stay was 13 days (IQR: 11-26 days). No patients were readmitted to the hospital within 30 days after discharge.

Histopathological evaluation of the resection specimen showed that a radical resection was achieved in 64% (9/14). The median lymph node yield was 21 (IQR: 12-26).

Acute surgical interventions for gastric cancer

An acute surgical intervention for gastric cancer was performed in 159 patients, with an upfront curative intent in the majority of patients (70%). The median time between diagnostic biopsy and acute surgery was 23 days (IQR 11 – 36 days). Histological confirmation of gastric cancer was not present prior to surgery in 25 patients (16%). The reason for surgery was a bleeding in 68 patients (43%), perforation in 19 patients (12%) and other (not specified) in the remaining 73 patients (46%). Gastrectomy was performed in 122 patients (77%), which was by a minimally invasive approach in 39 patients and by an open approach in 83 patients. The remaining 37 patients (23%) underwent a surgical procedure without resection, which involved a gastroenterostomy in 26 patients, diagnostic laparoscopy in 6 patients and a diagnostic laparotomy in 5 patients. Most minimally invasive procedures were observed in the more recent years (Figure 2). A complete overview of patient and treatment-related characteristics of the gastric cancer patients is presented in Table 3.

Perioperative and oncological outcomes of the 122 patients who underwent a gastrectomy are shown in Table 4. Conversion to an open procedure occurred in 9 of the 39 minimally invasive gastrectomies (23%), mostly because of the extent of the tumor and poor exposure (Table 4). Postoperative complications occurred in 14 of the 39 patients who underwent a minimally invasive gastrectomy (36%) and in 42 of the 83 patients who underwent an open gastrectomy (51%). When comparing minimally invasive gastrectomy versus open gastrectomy, pulmonary complications occurred in 13% versus 18%, anastomotic leakage in 8% versus 8%, and wound infection in 0% versus 13%, respectively. Re-interventions, mostly for anastomotic leakage in both groups, were performed in 23% after a minimally invasive gastrectomy versus 14% after an open gastrectomy. Postoperative mortality occurred in 8% after a minimally invasive gastrectomy versus 11% after an open gastrectomy. The median length of hospital stay was 9 days (IQR: 7-16 days) after minimally invasive gastrectomy versus 11 days (IQR: 7-17 days) after open gastrectomy. Readmission to the hospital was seen in 8% after minimally invasive gastrectomy versus 11% after open gastrectomy.

12

Histopathological evaluation of the resection specimen showed that a radical resection was achieved in 34 of the minimally invasive gastrectomies (87%) and in 55 of the open gastrectomies (66%). The median lymph node yield was 21 (IQR: 15-32) after minimally invasive gastrectomy and 16 (IQR: 11-24) after open gastrectomy.

A

B
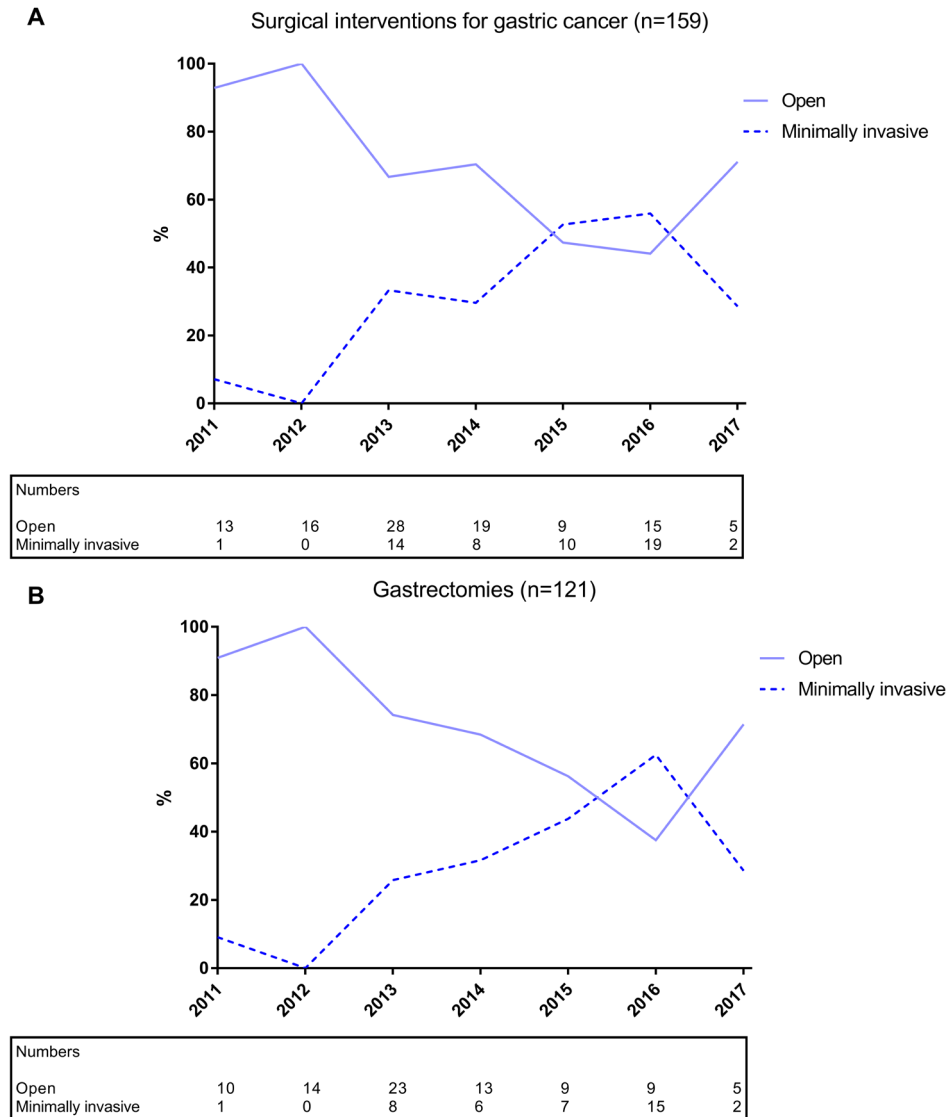
Figure 2. Minimally invasive and open surgical interventions (A) and gastrectomies (B) for acute presentation of gastric cancer in the study period.

Table 3. Baseline characteristics of patients who underwent an acute surgical intervention for gastric cancer in the Netherlands between 2011 and 2017.

Characteristics	Open		Minimally invasive	
	n = 105	%	n = 54	%
Patient-related characteristics				
Age, years (mean ± SD)	71 ± 10		71 ± 12	
Sex				
Male	79	75%	33	61%
Female	26	25%	21	39%
BMI, kg/m² (mean ± SD)	25 ± 4		25 ± 4	
ASA classification				
I	8	8%	2	4%
II	39	37%	25	46%
III	46	44%	23	43%
IV	7	7%	4	7%
V	1	1%	0	0%
Not specified	4	4%	0	0%
Comorbidities				
Cardiac	35	33%	24	44%
Vascular	42	40%	27	50%
Diabetes	22	21%	10	19%
Pulmonary	23	22%	11	20%
Previous abdominal or thoracic surgery	37	35%	18	33%
Tumor location				
Fundus	6	6%	3	6%
Corpus	28	27%	12	22%
Antrum	48	46%	22	41%
Pylorus	12	11%	12	22%
Stomach	3	3%	2	4%
Other/not specified	8	8%	3	6%
Histology				
Adenocarcinoma	88	84%	49	91%
Other	8	8%	4	7%
Not specified	9	8%	1	2%
cT status*				
T1	4	4%	2	4%
T2	8	8%	8	15%
T3	32	30%	20	37%
T4	18	17%	10	19%
Tx	43	41%	13	24%
cN status*				
N0	26	25%	19	35%
N+	46	44%	28	52%
Nx	33	31%	7	13%

12

Table 3. Continued

Characteristics	Open		Minimally invasive	
	n = 105	**%**	**n = 54**	**%**
cM status*				
M0	76	72%	44	81%
M1	9	9%	4	7%
Mx	20	19%	6	11%
Treatment-related characteristics				
Neoadjuvant therapy†				
None	93	89%	52	96%
Chemotherapy	11	10%	2	4%
Chemoradiotherapy	1	1%	0	0%
Setting				
Emergent (<12 hours)	37	35%	8	15%
Urgent (>12 hours)	68	65%	46	85%
Reason for acute surgery				
Bleeding	41	39%	26	48%
Perforation	17	16%	2	4%
Other	47	45%	26	48%
Surgical procedure				
Total gastrectomy	26	25%	8	15%
Partial gastrectomy	57	54%	31	57%
Bypass (gastroenterostomy)	17	16%	9	17%
Diagnostic laparotomy/laparoscopy	5	5%	6	11%
Intention				
Curative intent	74	70%	43	80%
Palliative intent	26	25%	8	15%
Not specified	5	5%	3	6%
Lymph node dissection	64	61%	35	65%
Year of surgery				
2011 – 2013	57	54%	15	28%
2014 – 2017	48	46%	39	72%

ASA American Society of Anesthesiologists; *BMI* body mass index at diagnosis; *SD* standard deviation
Note. Data are numbers of patients with column-based percentages in parentheses, unless otherwise stated.
* Clinical T status and N status are based on AJCC TNM 7th edition.
† The standard regimen for peri-operative treatment for gastro-esophageal junction or gastric adenocarcinoma generally consists of chemotherapy regimens similar to the MAGIC-trial (epirubicin, cisplatin and capecitabine).

Table 4. Short-term outcomes for patients who underwent an acute gastrectomy for gastric cancer in the Netherlands between 2011 and 2017.

	Open		Minimally invasive	
	n = 83	%	n = 39	%
Peroperative outcomes				
Conversion	NA		9	23%
Reasons for conversion	NA			
Tumor extent			4	10%
Poor exposure			4	10%
Peroperative complication			1	3%
Postoperative complications				
All*	42	51%	14	36%
Medical complications				
Pulmonary†	15	18%	5	13%
Cardiac‡	7	8%	2	5%
Thromboembolic§	4	5%	2	5%
Neurologic¶	4	5%	2	5%
Urologic#	4	5%	1	3%
Intra-abdominal complications				
Anastomotic leakage**	7	8%	3	8%
Abscess	4	5%	1	3%
Chyle leakage	0	0%	0	0%
Wound complications				
Fascia dehiscence	2	2%	0	0%
Wound infection††	11	13%	0	0%
Other	11	13%	5	5%
Reinterventions				
All*	12	14%	9	23%
Surgical	11	13%	6	15%
Radiologic	3	4%	2	5%
Endoscopic	2	2%	1	3%
Not specified	0	0%	1‡‡	3%
Causes for reinterventions				
Anastomotic leakage	5	6%	2	5%
Fascia dehiscence	1	1%	0	0%
Complication of feeding jejunostomy	0	0%	1	3%
No complication encountered	3	4%	2	5%
Other	3	4%	3	8%
Recovery				
ICU duration (median, IQR)	1	(0-2)	1	(0-1)
Length of stay (median, IQR)	11	(7-17)	9	(7-16)
Postoperative mortality §§	9	11%	3	8%
Readmission to hospital ¶¶	9	11%	3	8%

12

Table 4. Continued

	Open		Minimally invasive	
	n = 83	**%**	**n = 39**	**%**
Oncological outcomes				
Radicality				
R0	55	66%	34	87%
R1	14	17%	3	8%
R2	11	13%	0	0%
Lymph node yield (median, IQR)	16	(11-24)	21	(15-32)
Positive lymph nodes harvested (median, IQR)	4	(0-9)	5	(1-10)

IQR interquartile range, *NA* not applicable

Note. Missing values were encountered in ICU duration (n=12), length of stay (n=2), readmission (n=4), radicality (n=5), lymph node yield (n=2) and positive lymph nodes harvested (n=2).

* Defined as number of patients who experienced a postoperative complication or underwent a reintervention. One patient could experience more than 1 complication or reintervention.

[†] Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome.

[‡] Supraventricular and ventricular arrhythmia, myocardial infarction and/or heart failure.

[§] Pulmonary embolism, deep venous thrombosis, stroke and/or thrombophlebitis.

[¶] Acute delirium.

[#] Urinary tract infection, urinary retention and/or renal insufficiency.

** Any clinically or radiologically proven anastomotic leakage.

[††] Wound infection requiring drainage or antibiotic treatment.

[‡‡] Patient who underwent a reintervention for a complication of the feeding jejunostomy.

[§§] Death during initial hospital admission or within 30 days after surgery.

[¶¶] Readmission to hospital within 30 days after initial discharge.

Discussion

In this nationwide cohort study concerning patients who underwent acute surgery for esophageal and gastric cancer, short-term postoperative and oncological outcomes of minimally invasive resections were comparable to open resections.

Previous studies have shown the safety and feasibility of minimally invasive surgery for esophagogastric cancer in the elective setting.[3,4,12,11,5–10] For esophageal cancer, minimally invasive esophagectomy resulted in a shorter hospital stay, higher lymph node yield, similar radical resection rate and postoperative pulmonary complications, but higher reintervention rates in several population-based studies.[5–8] Due to the low number of acute esophagectomies, it was unfortunately not possible in this study to perform the analyses that would be required to reproduce these results for minimally invasive esophagectomy in the acute setting. For gastric cancer, minimally invasive gastrectomy in the elective setting was deemed to be safe and feasible regarding overall postoperative morbidity and mortality rates, as well as short-term oncological outcomes, and resulted in decreased wound complications and a shorter hospital stay compared to open gastrectomy.[12,10] The current study of minimally invasive gastrectomy in the acute setting also demonstrated comparable

oncological outcomes to the open approach, as well as a potentially decreased median length of hospital stay. However, the current study demonstrated a higher conversion rate of minimally invasive gastrectomies in the acute setting (23% versus 0.9%[12], 3.5%[11] and 10%[10] in the elective setting), as well as a potentially increased percentage of patients that underwent a reintervention after minimally invasive gastrectomy (23% versus 14% in the acute setting and 0.4% versus 0.4%[11], 1.2% versus 1.5%[12] and 17% versus 16%[10] in the elective setting for minimally invasive gastrectomy versus open gastrectomy, respectively). Unfortunately no clear explanation for this difference could be deduced from the causes for the reinterventions as available in the data.

In order to correctly interpret the current results, it must be noted that esophagogastric cancer surgery has been centralized since 2011 in the Netherlands. This is one of the main reasons that 84% of the elective esophagectomies and 40% of the elective gastrectomies are performed by minimally invasive techniques in the recent years.[6,9] A similar increase has been seen for the use of minimally invasive techniques in the acute setting. Most surgeons in the Netherlands implemented these techniques after participating in a hands-on course on minimally invasive esophagectomy and gastrectomy, followed by several cases with an experienced surgeon present. The influence of centralization and learning curves on postoperative outcomes also seem to be important in for esophagogastric surgery in the acute setting, as demonstrated by a recently published study from England.[16] High-volume cancer centers and surgeons are more experienced in managing patients following esophagectomy and gastrectomy, and have the appropriate infrastructure available.[16] As such, they might be better equipped to deliver consistent levels of high-quality outcomes for minimally invasive surgery in the acute setting as well which might explain the comparable outcomes for minimally invasive and open surgery in the current study.

Overall, acute surgical interventions for upper gastrointestinal malignancies are rare, accounting for only 2% of all surgical interventions for upper gastrointestinal malignancies in the Netherlands. This especially applies for surgical interventions for esophageal cancer, occurring approximately once yearly in a country with an incidence of approximately 2500 new esophageal cancer cases per year.[17] Interestingly, most patients who underwent an acute surgical intervention had prior histological confirmation of their cancer diagnosis, indicating that patients generally did not present with an acute symptom of an unknown malignancy. The majority of the gastric cancer cases had a cause for acute intervention other than bleeding or perforation. As the DUCA registry only registers the indication for acute intervention in 3 prespecified categories (bleeding, perforation and other), the frequency of obstruction as another important indication for acute surgical interventions in gastric cancer could not be researched. However, in patients with an obstruction, a gastroenterostomy or distal gastrectomy might have been more frequently performed. When the surgical procedures of patients without a specified reason for the surgical

12

intervention are explored in more detail, it might indeed be that obstruction accounts for a large share of the not specified indications, as 30% of them underwent a gastroenterostomy (21/71) and 44% underwent a partial gastrectomy (31/71) (data not shown).

The population-based design with virtually complete inclusion of all patients in the Netherlands is a significant strength of the study, along with the prospective data collection and detailed information on strictly defined postoperative outcomes. However, there are some limitations of the current study that need to be addressed. First, the small numbers of patients in all groups precluded a direct comparison between minimally invasive and open surgery correcting for bias. This prevents firm conclusions to be drawn regarding the potentially observed benefits of minimally invasive compared to open surgery in the acute setting (e.g. the decreased median length of hospital stay, higher observed percentage of radical resections and increased median lymph node yield), as well as regarding the potential disadvantages of minimally invasive surgery (e.g. the increased percentage of reinterventions after minimally invasive gastrectomy compared to open gastrectomy). Second, the introduction of minimally invasive surgery for upper gastrointestinal malignancies occurred simultaneously with centralization of cancer care and the introduction of enhanced recovery after surgery (ERAS) programs in the Netherlands. It has been shown that centralization of surgery is associated with reduced complications and improved long-term survival[18-21] and that the use of ERAS programs protocols can reduce the length of hospital stay.[22,23] As such, the observed outcomes in this study for both minimally invasive as open surgery are probably influenced by these factors. It must be further acknowledged as a limitation that, due to the privacy restrictions of the national database, individual hospital related factors such as postoperative management protocols and background experience in minimally invasive surgery might have influenced the results but were not available. This also applies to more detailed information regarding the reasons for surgical intervention, such as iatrogenic versus spontaneous perforations and the severity of the bleeding. Lastly, no long-term survival data is available for the patients in the DUCA registry.

Future research regarding this topic would benefit from an even larger cohort study that would allow for statistical analyses corrected for bias to compare minimally invasive surgery and open surgery for esophagogastric cancer in the acute setting. However, considering the rarity of these events, larger case series are probably difficult to find.

In conclusion, this nationwide cohort study demonstrates that acute surgical interventions for esophageal and gastric cancer are rare. For gastric cancer, minimally invasive surgery appears to be feasible and safe in the acute setting with at least comparable postoperative clinical and short-term oncological outcomes compared to open surgery, but a relatively high conversion rate.

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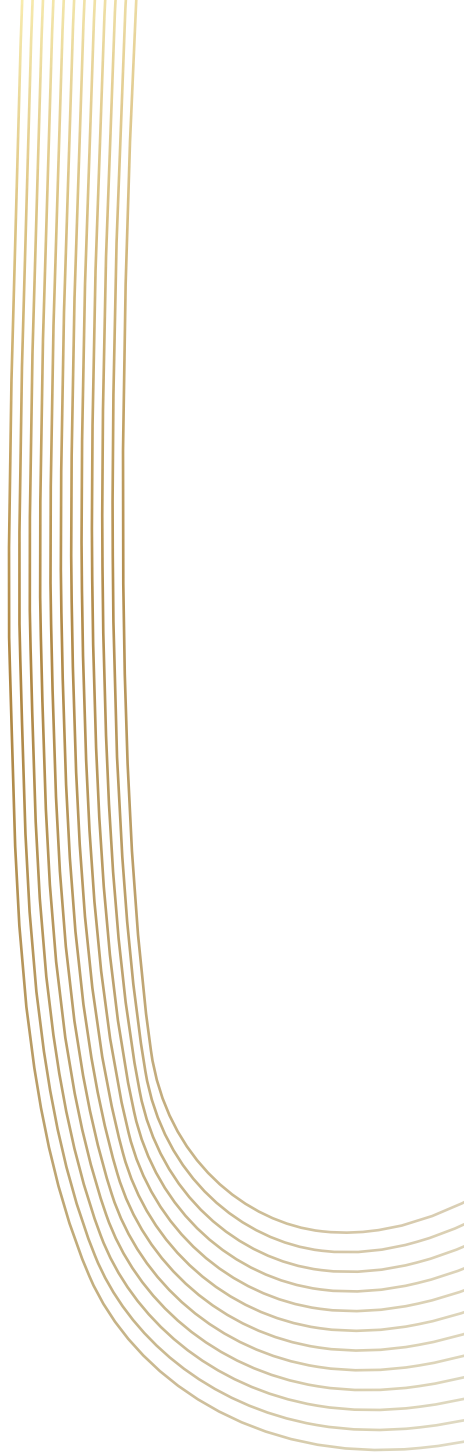
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PART IV

Summary and general discussion

Chapter 13

Summary

Esophageal cancer affects almost 600 000 people per year worldwide. Although the prognosis of patients with esophageal cancer has improved over the past decades, treatment still has a detrimental impact on a patients' quality of life. Personalized medicine is rapidly gaining popularity for esophageal cancer, but largely remains a philosophy rather than clinical practice due to limited evidence on accurate treatment response assessment and personalized treatment strategies. As such, the research presented in this thesis aimed at improvements in neoadjuvant chemoradiotherapy (**part I**), treatment response assessment (**part II**) and surgical treatment (**part III**) in patients with esophageal cancer.

Neoadjuvant chemoradiotherapy

Part I of this thesis focused on optimizing treatment efficacy rates of neoadjuvant chemoradiotherapy while balancing the toxicities, and provided insight in the consequences of toxicities of neoadjuvant chemoradiotherapy for the patient.

Chapter 2 described the impact of neoadjuvant chemoradiotherapy and related adverse events on short-term health-related quality of life. The negative effect of neoadjuvant chemoradiotherapy appeared to be most pronounced on physical functioning and fatigue, whereas a positive effect was observed in odynophagia at 1 month follow-up. General health-related quality of life remained similar. Adverse events during neoadjuvant chemoradiotherapy had a negative effect on social functioning, dysphagia, pain and taste at follow-up. This information could be used by physicians to adequately manage patients' expectations about their quality of life during neoadjuvant chemoradiotherapy, so that patients can anticipate on these effects and take well informed treatment decisions.

As a first step towards minimizing toxicity rates of neoadjuvant chemoradiotherapy by means of real-time tumor tracking and personalized tumor margins during radiotherapy, **chapter 3** researched variations in intra-fraction motion. Patients undergoing neoadjuvant chemoradiotherapy for esophageal cancer underwent 6 sequential MRI scans. To quantify intra-fraction motion, 2 cine-MRI series were acquired with approximately 10 minutes interval, both in coronal and sagittal plane. Intra-fraction motion was found to be highly variable between and within patients with esophageal cancer during neoadjuvant chemoradiotherapy. The stochastic nature of the tumor drift indicated that real-time tumor motion management during radiotherapy is a prerequisite to safely reduce radiotherapy margins.

The multi-institutional analysis in **chapter 4** researched whether neoadjuvant radiation dose increases pathologic response rates in esophageal cancer patients. A possible strategy for treatment intensification could be to increase the neoadjuvant radiation dose and the available studies that assess whether neoadjuvant radiation dose influences tumor response

rates are equivocal. No radiation dose response relation was observed for pathologic complete response. However, pathologic major response (defined as patients with a pathologic complete response and patients with a near-complete response) might be impacted by neoadjuvant radiation dose. Further prospective trials are needed to evaluate a potential survival benefit.

Treatment response assessment

Accurate assessment of response to neoadjuvant chemoradiotherapy is important for safe implementation of an organ-sparing approach in pathologic complete responders, but also to adapt treatment strategies in expected poor responders. Studies researching the performance of a multimodality imaging approach for treatment response assessment were presented in **part II** of this thesis.

Chapter 5 described the distinct and combined value of ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG PET-CT) and diffusion-weighted (DW) magnetic resonance imaging (MRI) for treatment response prediction. This prospective international multicenter study demonstrated that changes on ^{18}F-FDG PET/CT *after* neoadjuvant chemoradiotherapy and early changes on DW-MRI *during* neoadjuvant chemoradiotherapy can help identify pathologic complete responders to nCRT in esophageal cancer. Moreover, ^{18}F-FDG PET/CT and DW-MRI might be of complementary value in the assessment of pathologic complete responders. When combining both modalities, patients with a pathologic complete response could be accurately discriminated from patients without a pathologic complete response in 83% of the patients (c-statistic: 0.83).

The potential of DW-MRI for treatment response assessment was further discussed in **chapter 6**. In this prospective study, patients underwent 6 DW-MRI scans: 1 baseline scan before starting neoadjuvant chemoradiotherapy and weekly scans during 5 weeks of neoadjuvant chemoradiotherapy with the aim to establish the optimal timing of DW-MRI scanning during neoadjuvant chemoradiotherapy for the prediction of pathologic complete response. The relative change in tumor apparent diffusion coefficient (ΔADC(%)) as measured on DW-MRI during the first 2 weeks of neoadjuvant chemoradiotherapy was the most predictive for pathologic complete response. These results could further aid the minimization of the burden of repeated scanning for patients, as well as optimal usage of the available (financial) resources, while assuring the best predictive ability of DW-MRI.

Chapter 7 provides the rationale and study protocol for a nationwide, prospective study with the aim to develop a multimodal prediction model that predicts the patients' individual probability of a pathologic complete response after neoadjuvant chemoradiotherapy for

13

esophageal cancer. In this observational trial (PRIDE study) recruiting 200 patients, patients will undergo 3 ^{18}F-FDG PET-CT scans and 3 MRI scans before, during and after treatment with neoadjuvant chemoradiotherapy. Additionally, blood samples are obtained at the same 3 time points for the analysis of the presence of circulating tumor DNA (ctDNA) and an endoscopy with biopsies as well as an endoscopic ultrasonography after finishing neoadjuvant chemoradiotherapy. Accurate prediction of response to neoadjuvant chemoradiotherapy could lead to a patient-tailored approach with omission of surgery in the future in case of predicted pathologic complete response, potentially improving quality of life and reducing health care costs. Furthermore, additional neoadjuvant treatment might be offered to poor responders.

Lastly, **chapter 8** evaluated the burden of repeated MRI and PET-CT scanning during neoadjuvant chemoradiotherapy from the perspective of the patient. In this study, 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. When asked to rank different examinations, patients preferred MRI over PET-CT. As such, both MRI and PET-CT are generally well-tolerated from a patient perspective and could be used for the assessment of response to treatment in esophageal cancer patients.

Surgical treatment

Part III of this thesis addressed the surgical treatment of esophageal cancer patients in the era of multimodality management.

The narrative review in **chapter 9** provides an extensive outline of the literature on surgical treatment in the era of multimodality management of esophageal cancer. Although esophagectomy is still considered the cornerstone of curative treatment for locally advanced esophageal cancer, it remains associated with considerable postoperative morbidity, despite promising results of minimally invasive techniques. In this light, both physical status and response to neoadjuvant therapy are important factors for selecting patients who will benefit from surgery. Furthermore, it is important to optimize the entire perioperative trajectory: from the initial outpatient clinic visit to postoperative discharge. Enhanced Recovery After Surgery (ERAS) is increasingly recognized for esophagectomy and emphasizes perioperative aspects such as nutrition, physiotherapy, and pain management.

Despite its prognostic benefits, neoadjuvant chemoradiotherapy for resectable esophageal cancer is accompanied by the risk of treatment-associated toxicities. This is especially relevant when these toxic effects prevent patients from undergoing surgical resection. By means of a population-based study including all patients from the Netherlands who started

neoadjuvant chemoradiotherapy for esophageal cancer in 2015-2016 as described in **chapter 10**, it was demonstrated that 1 in 7 patients who started neoadjuvant chemoradiotherapy eventually does not proceed to surgical resection. These patients have a lower overall survival compared to the patients who undergo neoadjuvant chemoradiotherapy followed by surgical resection. These findings could be a starting point for further research, which should aim to investigate whether this patient group can be selected prior to treatment, and whether patient-individualized treatment, centralization of oncological care and counseling will result in a larger proportion of patients who will undergo surgery.

Chapter 11 builds on previous research by our group concerning atherosclerotic calcification as measured on routine diagnostic CT scans as a risk factor for the development of anastomotic leakage – a severe complication – following esophagectomy. In order to study whether this association derived from local flow limitations or vascular disease in general, diagnostic CT images of esophageal cancer patients were scored for the presence of arterial calcification on 10 locations based on a visual grading system and related to anastomotic leakage. Calcification of the coronary and supra-aortic arteries on routine CT were predictive of cervical anastomotic leakage after esophagectomy. These results suggested that generalized cardiovascular disease is a strong indicator for the risk of leakage. This new described risk factor may be used in future prediction models, and eventually aid to a more individualized identification of the risk of anastomotic leakage following esophagectomy.

With the rise of minimally invasive surgery in the elective setting, the safety and feasibility of minimally invasive esophagectomy and gastrectomy in the acute setting was assessed in **chapter 12**. This nationwide study including data from the Dutch UpperGI Cancer Audit (DUCA) between 2011 and 2017 demonstrated that acute resections for esophageal cancer were very rare. As these numbers were very low, no comparison between minimally invasive and open esophagectomies was made. Minimally invasive gastrectomy however was at least comparable to open gastrectomy regarding postoperative complications and oncological outcomes. As such, it was deemed safe and feasible in the acute setting.

In conclusion, the research presented in this thesis provides encouragement for individualized treatment for esophageal cancer patients by means of multimodality treatment response assessment using ^{18}F-FDG PET/CT and DW-MRI, balancing treatment efficacy and toxicity of neoadjuvant therapy, and more appropriately perform risk-stratification of patients for surgery following neoadjuvant therapy.

13
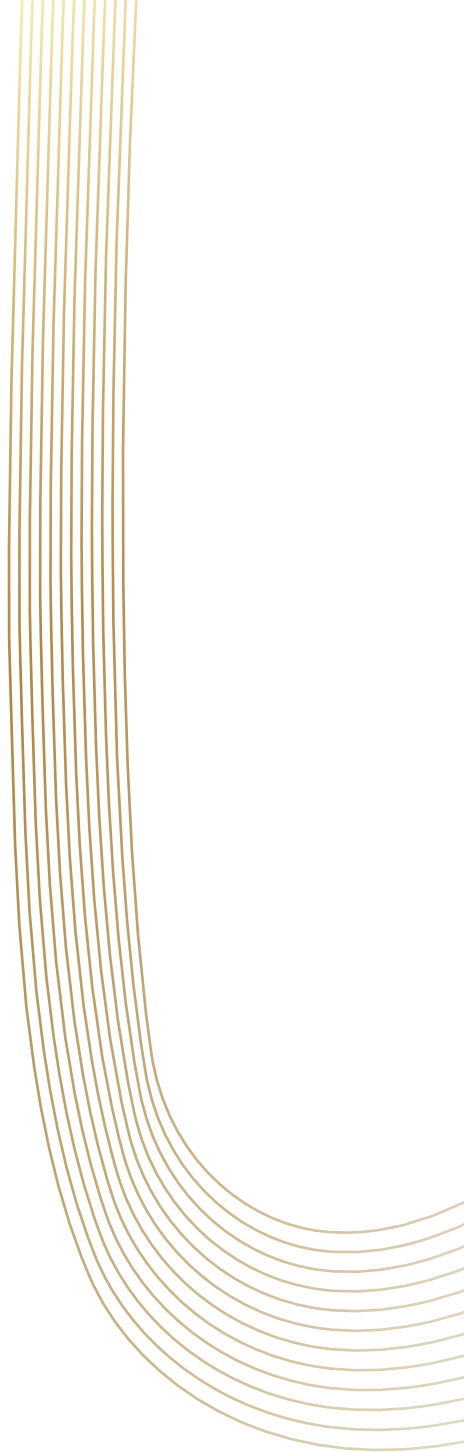
Chapter 14

General discussion and future perspectives

The treatment of locally advanced esophageal cancer is increasingly shifting towards individualized strategies that are based on developments within the fields of neoadjuvant therapy and surgery. The aim of this thesis was to establish evidence to guide individualized decision-making for esophageal cancer patients by assessing the impact and efficacy of neoadjuvant chemoradiotherapy (**part I**), improving treatment response assessment (**part II**) and refining surgical treatment (**part III**). In this final chapter, the implications of the findings for current and future clinical practice are discussed.

Neoadjuvant treatment

In most countries, patients with locally advanced esophageal cancer undergo neoadjuvant chemoradiotherapy or chemotherapy before esophagectomy. Neoadjuvant chemoradiotherapy is the widely accepted treatment of choice for patients with esophageal squamous cell carcinoma, whereas the optimal multimodality regimen remains topic of debate for patients with adenocarcinoma. Hence, worldwide variation exists on the preferred neoadjuvant treatment strategy. While many European centers use neoadjuvant chemoradiotherapy (nCRT) according to the CROSS regimen (carboplatin/paclitaxel with concurrent 41.4 Gy)[1], neoadjuvant radiation dosages are generally higher (50.4 Gy) and combined with 5-fluorouracil and taxane or with platinum-based compounds in North-America. Neoadjuvant or perioperative chemotherapy regimens vary as well; the OEO2[2], MAGIC[3] and FNCLCC/FFCD[4] regimens are all commonly used. This section discusses the relevant considerations in the search for the optimal neoadjuvant treatment strategy for esophageal cancer.

Balancing benefits and toxicity
Neoadjuvant treatment should ideally prolong survival while avoiding treatment-related burden. The survival benefit of neoadjuvant therapy in the treatment of locally advanced esophageal cancer has been repeatedly demonstrated, as both disease-free and overall survival were shown to increase when compared to surgery alone.[5,6] Even so, treatment-related toxicity might impact quality of life and is therefore important to be considered. In this context, chapter 2 investigated the impact of neoadjuvant chemoradiotherapy on short-term health-related quality of life (HRQOL) in patients undergoing curatively intended treatment for esophageal cancer, showing that impairments in HRQOL were generally limited and mostly involved physical functioning and fatigue, which is in line with previous research.[7-9] However, in patients who suffered from adverse events during neoadjuvant chemoradiotherapy, a significant decline in HRQOL was observed. These findings emphasize the need to identify ways to reduce adverse events and toxicity during neoadjuvant treatment.

Treatment-related toxicity of neoadjuvant chemoradiotherapy might be reduced by margin reduction during radiation therapy, aiming at avoiding radiation to surrounding organs at risk. Previous studies demonstrated that radiation of the heart and lungs during neoadjuvant treatment for esophageal cancer has a negative impact on overall survival.[10] MRI-guided radiation delivery and proton therapy may improve targeted irradiation of the tumor while sparing surrounding organs at risk from high radiation dosages.[11–13] These techniques have been recently introduced and are currently being investigated for several cancer types, including esophageal cancer. Some evidence has already been generated for the use of proton therapy in esophageal cancer: an observational cohort study reported comparable efficacy in combination with lower rates of treatment-related toxicity in comparison to photon therapy.[14] Future studies will need to determine the potential clinical advantage of proton therapy and MRI-guided radiation delivery in terms of reducing treatment-related toxicity and improving treatment efficacy in the neoadjuvant treatment for esophageal cancer.

Next to reducing treatment-related toxicity, researchers should also strive to maximize the efficacy of neoadjuvant chemoradiotherapy. Radiation dose escalation might be interesting, particularly for the relatively large proportion of patients with a near-complete response after neoadjuvant chemoradiotherapy (19%), as these patients have a decreased survival compared to pathologic complete responders. Hence, increasing pathologic complete response rates is an important aim of current research. Radiation dose escalation might be performed by means of simultaneous integrated boost techniques or sequential boost techniques. Studies using simultaneous integrated boost techniques have thus far demonstrated the potential of improved locoregional control rates in esophageal cancer.[15,16] Sequential boost techniques might even be preferable, as these allow for response based dose-escalation. A recently published phase I trial established the feasibility and safety of a cumulative tumor dose of 86 Gy in locally advanced esophageal squamous cell carcinomas, using hyperfractionated radiation therapy following standard-dose chemoradiotherapy.[17] Late esophageal toxicity was relatively infrequent and mild in this study[17], which is in contrast to the findings of the RTOG 9207 study, which intensified radiotherapy with esophageal brachytherapy and reported an unexpectedly high incidence (14%) of esophageal fistulas (1 aortoesophageal, 3 esophageal-bronchotracheal and 2 esophageal-mediastinal fistulas).[18] Future studies on radiation dose escalation in esophageal cancer should focus on partial responders to neoadjuvant chemoradiotherapy or patients with squamous cell carcinomas (as these are more radiosensitive than adenocarcinomas) in light of an organ-sparing approach for these patients. Non-responders and adenocarcinomas are more likely to benefit from alternative therapies instead of higher radiation dosages.

14

Alternatives to neoadjuvant chemoradiotherapy

Alternative therapies to neoadjuvant chemoradiotherapy include perioperative chemotherapy and targeted therapies. The FLOT4 trial recently showed that perioperative chemotherapy with the FLOT regimen (docetaxel, oxaliplatin, leucovorin, and 5-FU) was associated with increased survival in patients with gastric or gastro-esophageal adenocarcinoma compared to the ECF/ECX triplet regimen (epirubicin, cisplatin, and 5-FU or capecitabine).[19] It should be noted, however, that almost half of the included patients had gastric adenocarcinoma, which might imply that the results cannot be generalized to the esophageal cancer population. Several randomized trials are now comparing perioperative chemotherapy and neoadjuvant chemoradiotherapy for esophageal cancer (NeoAegis[20], ESOPEC[21], CMISG1701[22], NEOSCOPE[23], PROTECT-1402[24]), which are expected to provide more clarity in the near future.

Besides chemotherapy and radiotherapy, targeted anticancer therapies such as human epidermal growth factor receptor 2 (HER2) antibodies (trastuzumab, pertuzumab) and vascular endothelial growth factor receptor (VEGFR)-2 antibodies (ramucirumab) are emerging. Moreover, the addition of immunotherapeutic strategies to neoadjuvant chemoradiation or perioperative chemotherapy is currently being evaluated, such as programmed death ligand 1 (PD-L1) targeted therapy with atezolizumab or pembrolizumab.[25] These immunotherapeutic strategies have great potential, but a much better understanding of the immune microenvironment underlying esophageal squamous cell and adenocarcinoma is needed if we are to exploit the inherent cancer fighting capabilities of each individual patient's immune system.[25]

Although surgery combined with adjuvant treatment might not be expected to yield survival benefits for the overall esophageal cancer population[26], it might make sense to selectively administer adjuvant therapy to patients who have first been treated with neoadjuvant therapy followed by esophagectomy. As esophageal cancer patients with nodal metastases are likely at high risk for micrometastatic systemic disease and disease recurrence following surgical resection, it seems biologically plausible that adjuvant therapy could result in survival benefit in this subgroup. In patients with residual nodal disease (ypT0-4N+) following neoadjuvant chemoradiotherapy and esophagectomy, adjuvant chemo- or radiotherapy have been suggested to improve survival.[27,28] However, these findings need to be confirmed, ideally in a formal randomized controlled trial, before routine application in clinical practice can be recommended.

The abovementioned considerations and suggestions for improvement of treatment efficacy and decreasing the burden of treatment have been summarized in Figure 1.
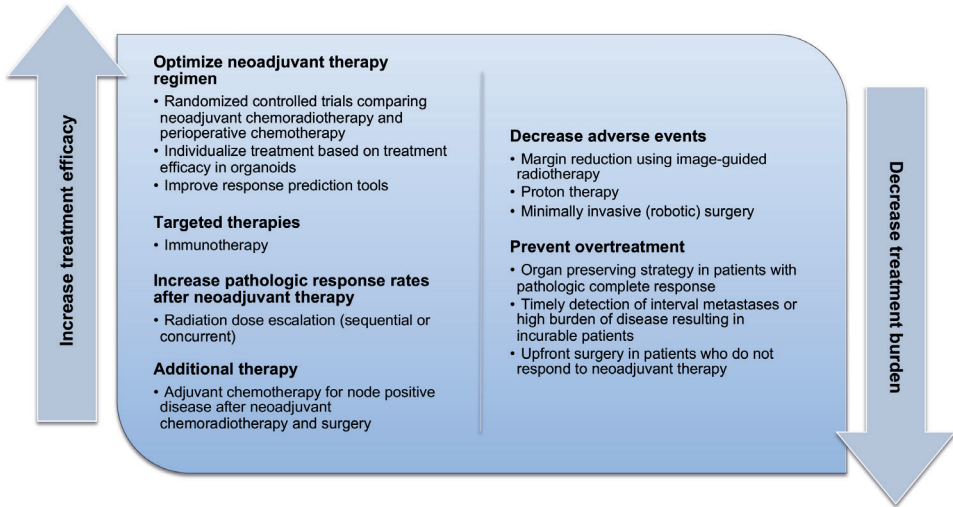
Figure 1. Summary of improvements to balance efficacy and burden of treatment in esophageal cancer patients

Treatment response assessment

Following neoadjuvant chemoradiotherapy, 20-30% of esophageal cancer patients have been reported to have a pathologic complete response.[1] A pathologic complete response represents the absence of viable tumor cells in the resection specimen after esophagectomy, and yet, these patients were subjected to a highly complex and invasive surgical procedure. These patients may benefit more from an active surveillance policy, in which frequent diagnostic evaluations after completion of neoadjuvant chemoradiotherapy may facilitate safe implementation of an organ-sparing approach. Conversely, patients with a poor response to neoadjuvant chemoradiotherapy (18%) are likely to benefit less or not at all from neoadjuvant chemoradiotherapy, but are exposed to its side-effects.[1] In these patients, ineffective therapy might be stopped and/or alternative treatment strategies (e.g. additional neoadjuvant treatment or upfront surgery) might be explored.

An interesting framework towards a more individualized approach for patients with an assumed pathologic complete response after chemoradiotherapy has been suggested earlier.[29] Roughly 3 main questions are to be answered before an individualized approach might become reality. First, what is the accuracy is of clinical restaging, and which diagnostic modalities should be used? Second, what is the risk of surgery for this patient based on his preexistent comorbidities, functional status after neoadjuvant chemoradiotherapy and objective evaluation of a preoperative workup (e.g. pulmonary function testing)? And third, what is the risk of surveillance for this patient, including the consequences of missed

14

residual cancer and salvage surgery?[29] And above all, how accurately can all these risks be predicted for an individual, and how should these risks and benefits be weighed?

A high level of confidence in predicting pathologic complete response is a must for implementing an esophageal preservation strategy, but accurate treatment response assessment is a very complex endeavor. Several diagnostic modalities – including diffusion-weighted magnetic resonance imaging (DW-MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (^{18}F-FDG PET-CT) as discussed in this thesis – have shown potential for response evaluation, but do not yet provide satisfactory results to justify clinical decision-making. Important remarks when reflecting upon the results of the studies on treatment response assessment as presented in this thesis and its corresponding possibilities, are amongst others the (technical) challenges in the use of advanced imaging techniques, heterogeneity in outcome evaluation and the risks of disease recurrence in pathologic complete responders.

Opportunities for image-guided response assessment

Traditionally, imaging end points have been limited to unidirectional size measurements, as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[30] However, biomarkers that inform on changes in tumor cellular architecture and functional characteristics are increasingly being explored.[30] DW-MRI is a functional imaging modality that allows for tissue characterization by deriving image contrast from restriction in the free diffusion (i.e. random mobility or Brownian motion) of water molecules, which is related to microstructural tissue organization. An apparent diffusion coefficient (ADC) map can be derived from the DW-MRI images to quantify the diffusion restriction in a certain volume of interest. The ADC is inversely correlated with tissue cellularity. As chemoradiotherapy can result in the loss of cell membrane integrity, tumor response can be detected as an increase in tumor ADC. The studies presented in this thesis (chapter 5 and 6) rely on relative differences in ADC values as predictors for response to during neoadjuvant chemoradiotherapy.

The second modality under research in this thesis is ^{18}F-FDG PET-CT, which depends on the increased accumulation of ^{18}F-FDG within tumorous tissue relative to normal tissue.[31] Changes in the accumulation of ^{18}F-FDG have been shown to be useful as an imaging biomarker for assessing response to treatment, for which the standardized uptake value (SUV) is frequently applied as a measurement of relative tissue/organ uptake.[31] This measure compensates for the amount of injected FDG and the patient size, and as such facilitates comparisons between patients.[31] The results of DW-MRI and ^{18}F-FDG PET-CT for treatment response assessment presented in this thesis are promising, but several opportunities for improvement remain in image-based assessment of pathologic response to treatment.

First, whole-tumor summary statistics (such as mean ADC or SUV values) are easily

applicable, but fail to fully address the important issue of tumor heterogeneity.[32] Voxel-based analytical methods, where changes in individual voxels can be monitored, may provide more precise results for response assessment.[33]

Second, cardiac triggering and respiratory gating techniques have been introduced to improve image quality by reducing motion artifacts.[34] Even when applying these techniques, insufficient scan quality led to the exclusion of up to 9% of patients from analyses presented in this thesis due to inadequate tumor visibility. As such, improved motion management techniques in future studies may facilitate substantial improvements in pathologic complete response prediction.

Third, ADC values are frequently calculated based on a mono-exponential fit on 3 b-values (diffusion weights). However, as signal decay as a function of b-values is not a mono-exponential process and depends on perfusion in the lower range of b-values[35], intravoxel incoherent motion (IVIM) as a method by which the diffusion component can be separated from the perfusion component may allow for a more precise assessment of the tumor and might contribute to characterizing differentiation grades and response rates of esophageal cancer in the future.[36]

Improve clinical applicability of image-guided response assessment
So far, the use of the aforementioned quantitative image-guided methods for response assessment in esophageal cancer is quite time-consuming. Clinical applicability could be improved by minimizing the duration of scan processing, standardization of imaging protocols as well as automatic delineation of tumor volumes on the scans. A first step forward is the use of semi-automated volumetric delineation methods (applied in chapters 5 and 6), of which the interobserver reproducibility of tumor delineations on DW-MRI and ADC measurements has shown to be very good.[33,37]

Clinical applicability could also be improved by a visual radiological assessment for residual disease on (DW-)MRI and ^{18}F-FDG PET-CT scans after neoadjuvant chemoradiotherapy. A pilot study including 51 esophageal cancer patients has pursued such an approach for MRI, resulting in high sensitivity (90-97%) – reflecting a low chance of missing residual disease after neoadjuvant chemoradiotherapy –, but low specificity (42-50%). This results in overstaging of complete responders as having residual tumor and, consequently, overtreatment.[38] Also, the interobserver agreement between 3 readers was only 0.55-0.71.[38] As such, this method is not yet ready for routine use in clinical practice but standardized guidelines on the image-based assessment of residual disease could improve these results in the future.

Ideally, a fully automatic tumor contouring tool (which is currently explored by the MD Anderson Cancer Center) would facilitate fast extraction of important features without human intervention and thus eliminate interobserver variation. In combination with the

14

emerging field of radiomics – the extraction of a large amount of features from radiographic medical images using data-characterization algorithms – and the possibility of sharing large imaging datasets, this field of research has the potential to uncover disease characteristics that fail to be appreciated by the naked eye. Ultimately, the aim is to develop a setting in which such an automatic contouring and feature extraction tool is an integrated element of radiology programs radiologists use to evaluate clinical progress during a multidisciplinary tumor board meeting. This element should automatically contour the tumor volume, deliver corresponding ADC, SUV and radiomic values and use these values for a prediction model (such as presented in chapter 5 and 6, and currently under development by the study described in chapter 7). This model should translate these features into a predicted probability of a pathologic complete response or poor response based on those clinical and imaging characteristics, which should subsequently be discussed with the patient in order to make treatment decisions.

Alternatives to image-guided response assessment
Next to ^{18}F-FDG PET-CT and DW-MRI, endoscopic assessments with (bite-on-bite) biopsies after neoadjuvant chemoradiotherapy are frequently proposed to rule out potential residual cancer cells. Obviously, physicians would not want to withhold surgery in patients who have residual tumor cells based on biopsies after neoadjuvant chemoradiotherapy. For patients with negative biopsies however, the consequences are not so straightforward. As the distribution of residual cancer cells after chemoradiotherapy is unpredictable, and can be in the mucosal membrane, adventitia area or even in the lymph nodes, it is difficult to clinically detect residual chemoradiotherapy resistant tumors.[39,40] In a more recent study using bite-on-bite biopsies after neoadjuvant chemoradiotherapy, the proportion false-negative biopsies for the detection of TRG 3-4 tumors is still 10% (with a 95% confidence interval ranging from 4% to 23%).[41]
Additionally, circulating tumor DNA (ctDNA) – reflecting the presence and systemic burden of cancer – has emerged as a new valuable biomarker in the prediction of patient prognosis.[42–46]
In conclusion, the most useful studies are probably those that examine the combined ability of multiple restaging modalities. This approach is more pragmatic and provides the closest approximation of a provider's actual clinical approach to decision making. The Dutch PRIDE study (chapter 7) aims at determining the accuracy of various diagnostic modalities for pathologic complete response assessment in a large cohort of 200 patients and incorporates quantitative IVIM analyses and visual assessment of high-resolution DW-MRI with endoscopic assessments and ctDNA levels. Furthermore, 2 other large European trials (recruiting ≥ 200 patients) are currently studying the safety of active surveillance after a complete clinical response – as assessed with varying diagnostic modalities (the

Table 2. Summary of suggestions for improvements in treatment response assessment in esophageal cancer.

Cluster	Suggestions for improvements
General image-guided response assessment	Voxel-based analytical methods
	Full automatic delineation of tumor volume to increase reproducibility and reduce duration of assessment
MRI-based response assessment	Improve scan quality, e.g. the development of motion management techniques other than cardiac triggering and respiratory gating
	Bi-exponential model for ADC calculation (IVIM)
Alternatives to image-guided treatment response assessment	Endoscopic assessment of residual tumor with bite-on-bite biopsies
	Liquid biopsies (e.g. circulating tumor DNA)

French ESOSTRATE trial [NCT02551458] and the Dutch SANO trial [Netherlands Trial Register ID NTR6803]). The results of these 3 trials together will hopefully be practice changing, and lead to a patient-tailored wait-and-see approach with omission of surgery or upfront surgery in the appropriate patients.

Outcome evaluation

The success of treatment response assessment does not only depend on the diagnostic modalities under research, but also on the histopathologic assessment of complete response as an outcome variable. The success of pathologic tumor regression as an outcome variable depends on inter- and intraobserver variability, as well as standardization of regression grading systems. For pathologists, it is a difficult endeavor to determine whether residual tumor cells are actually viable tumor cells which might lead to disease recurrence[47], resulting in agreement varying from 0.44[48] to 0.73[49] for the Mandard tumor regression grading system in esophageal cancer. As there are many different grading systems of tumor regression after neoadjuvant therapy, experts call for a standardized system that homogenizes the application of tumor regression grading in gastrointestinal cancers.[47] It has to be a simple and reproducible system, for which a 4-tiered grading with the determination of the percentage of residual tumor was proposed.[47] For the correct assessment of pathologic response to treatment, it is furthermore very important that the entire tumor bed is embedded for histopathological analysis, as small residual tumor infiltrates in the periphery otherwise won't be detected.[50] This may lead to better comparability of studies focusing on surgery and medical oncology that include pathologic tumor regression as relevant parameter of treatment effects and outcome.[51]

Second, not only the degree of tumor regression in primary tumor is important, but also

14

tumor regression of tumor positive lymph nodes as these occur in up to 22% of patients with a pathologic complete response of the primary tumor after neoadjuvant chemoradiotherapy.[52–57] These patients have a decreased survival compared to patients without positive lymph nodes as a consequence.[52–57] Interestingly, the majority of these positive lymph nodes is situated within the neoadjuvant radiation field, possibly indicating a difference in radiosensitivity between the primary tumor and nodal metastases, but also between individual lymph nodes.[53] The differentiation between benign and malignant lymph nodes on MRI remains challenging as non enlarged nodes may harbor malignant cells and the field of view of the MRI scans is focused on the primary tumor instead of complete peri-esophageal tissue. Other response assessment tools, such as endoscopic ultrasonography with lymph node biopsies or ^{18}F-FDG PET-CT, should thus be added for the detection of lymph node metastases after neoadjuvant chemoradiotherapy.

Last, pathologic response is not 1-to-1 related with survival and – as stated before – survival is not the only patient-relevant outcome in oncologic research.[47] A clinical response to treatment might well be observed, but at the expense of worsening the patient's condition. HRQOL might even outweigh survival when deciding on treatment options[58], which led to the widespread incorporation of HRQOL and other patient-reported outcomes as an important endpoint when evaluating treatment efficacy.[59] This has already been executed by for example the previously mentioned ESOPEC trial, which compares nCRT versus preoperative chemotherapy for esophageal cancer.

Optimal care for clinical complete responders

As mentioned before, the risk of surveillance, including the consequences of missed residual cancer and salvage surgery, is an important factor when defining an individualized approach for patients with an assumed pathological complete response after chemoradiotherapy.[29] It is important to recognize that 20-40% of pathologic complete responders develop cancer recurrence within the 24 months after the completion of the trimodality strategy, irrespective of the histological subtype.[60–63] These patients might be eligible for salvage surgery, but the increased frequency and severity of postoperative complications is an emerging issue after salvage surgery.[40] There is also some evidence that salvage surgery is associated with a high proportion of tumor progression and worsened overall survival.[40] As such, patients and multidisciplinary tumor boards should be made aware of these differences in outcomes and salvage should be reserved for practice in high-volume institutions.[64]

Contrarily, some believe that a small amount of residual disease (<10%, TRG2) can initially be missed in clinical response assessment, as long as this residual disease is detected during active surveillance, while the tumor is still resectable.[65] The percentage of disease recurrence is however even higher in patients with a TRG2 than the already substantial number of 20-40% disease recurrence in pathologic complete responders, which questions whether

Table 3. Pitfalls and suggestions for improvement in the use of histopathologic treatment response assessment to neoadjuvant chemoradiotherapy as outcome variable for treatment efficacy in esophageal cancer

Pitfalls	Suggestion for improvement
Inter- and intraobserver variability between pathologists Lack of standardization of pathologic response rates	Consistent use of a 4-tiered simple and reproducible grading system
Single focus on primary tumor (pT status)	Include lymph node status (pN status) using other response assessment tools (such as EUS with biopsies or ^{18}F-FDG PET-CT)
Pathologic response is not 1-to-1 related with survival	Include survival as outcome variable in trials evaluating treatment response assessment

this is a valid assumption. This especially holds when during this time interval distant metastases develop. Also, the selection of a patient for active surveillance – and corresponding cost-intensive follow-up – who turns out to need delayed surgery because of disease recurrence would be the least beneficial from an economical perspective. As such, the cost-effectiveness of organ-sparing treatment is to be determined.

Several studies have been initiated comparing active surveillance versus upfront surgery after chemoradiotherapy (the French ESOSTRATE trial, the Korean ESOPRESSO trial and the Dutch SANO trial), of which the ESOPRESSO trial is so far the only published randomized trial including 86 patients. It was concluded that close observation with salvage surgery might be a reasonable option in terms of overall survival in patients with resectable esophageal squamous cell carcinoma achieving clinical complete response after chemoradiotherapy.[66] However, the patients included in this trial all had squamous cell carcinoma and treatment consisted of 2 cycles of induction chemotherapy and then chemoradiotherapy of 50.4 Gy in 28 fractions, which is not generalizable to the Western world. A retrospective propensity score matched study conducted in The Netherlands concluded that overall survival and progression free survival in patients with clinical complete response undergoing active surveillance or immediate surgery were not significantly different.[67] However, it is very important to realize that only 29 patients could be matched between both groups in this study, strongly questioning the validity of this conclusion for the entire esophageal cancer population.

Next to disease specific consequences of surveillance strategies, patients' preferences regarding active surveillance or standard esophagectomy when no residual cancer is observed after completion of neoadjuvant chemoradiotherapy should be taken into account when determining the optimal treatment strategy. A discrete choice experiment learned

14

us that substantial heterogeneity is observed in patients' preferences for either active surveillance or standard esophagectomy after a clinical complete response.[68] Also, for high risk surgical patients with significant comorbidities, a lower accuracy of a predicted pathological complete response might be deemed sufficient to postpone standard esophagectomy, whereas for younger, low risk surgical patients, a higher accuracy might be desired.

Risk-stratified treatment

Ultimately, we should aim for a risk-stratified selection of therapy based on local tumor response and the burden of distant disease in esophageal cancer patients. In this proposed risk stratified strategy, ctDNA levels might be determined in all patients with locally advanced esophageal cancer without apparent distant metastases upon clinical staging.

Patients with high ctDNA levels – representing a high burden of disease – might be offered induction chemotherapy tailored to either squamous cell carcinomas or adenocarcinomas, and patients with a good response might subsequently proceed to chemoradiotherapy. Patients with a poor response might need to switch their chemotherapy regimen, or could be included in novel trials, but should not proceed to the standard treatment pathway with chemoradiotherapy followed by esophagectomy.

Patients with low or undetectable ctDNA levels before treatment might be offered chemoradiotherapy directly. Following chemoradiotherapy, locoregional tumor response can be determined based on changes in MRI parameters (ΔADC(%)) half-way during chemoradiotherapy, ^{18}F-FDG PET-CT, endoscopic biopsy and ctDNA levels. This would lead to a further stratification between patients: patients with a good response on MRI and undetectable ctDNA levels might be locoregionally cured by chemoradiotherapy alone and might be offered an active surveillance strategy instead of surgery, potentially increasing quality of life with this organ-preserving strategy. Patients with a poor response on imaging but undetectable ctDNA levels after chemoradiotherapy will be offered surgical resection, as these probably still have residual locoregional disease. Lastly, patients with high ctDNA levels after chemoradiotherapy, irrespective of their response on imaging, might be offered chemotherapy, as high ctDNA levels might reflect occult metastatic disease and these patients thus might not benefit from surgical resection.

In summary, the need for individualized treatment based on response assessment to neoadjuvant chemoradiotherapy for esophageal cancer is clear. Several challenges in response assessment have been discussed and active surveillance strategies have been proposed. Both topics should be assessed in detail within trials the coming years to demonstrate whether a safe organ-sparing treatment strategy could become reality for a select group of patients with esophageal cancer.

Surgical treatment

With the implementation and favorable results of neoadjuvant therapy, curation is possible for an increased number of patients with esophageal cancer. Technical advances such as robot-assisted minimally invasive esophagectomy demonstrated to reduce the relatively high morbidity associated with esophagectomy, while enabling a safe and radical oncologic resection.[69] However, adequate staging and thorough examination of the general condition remain essential to select patients who are eligible for and would benefit from esophagectomy.

Accurate patient selection for surgery depends on tumor characteristics (such as TNM stage and tumor location), but also on assessment of comorbidities, patient nutritional status, and cardiopulmonary function. Recognition of the increased risk for not proceeding to surgery after starting neoadjuvant chemoradiotherapy or developing postoperative complications could aid the complex decision-making process of surgical treatment of patients with esophageal cancer. If this patient group can be selected prior to treatment, patient-individualized treatment (balancing the benefits and risks of esophagectomy for a specific patients), centralization of oncological care and counseling might result in a larger proportion of patients who will undergo successful esophagectomy.

The time between diagnosis and neoadjuvant chemoradiotherapy, as well as the interval between neoadjuvant chemoradiotherapy and esophagectomy, is highly suitable for interventions to optimize patients before surgery. Patients at high risk for not proceeding to surgery or postoperative complications could be more fully optimized before surgery by means of preventive measures, such as physical therapy to increase cardiorespiratory function and improvement of nutritional status.[70–72] The use of real world evidence in chapter 10 learned that age, BMI and performance status are risk factors for not proceeding to surgery after starting neoadjuvant chemoradiotherapy. Even though age as risk factors is not modifiable, the results could aid physicians in the identification of patients who might benefit from increased counseling in the preoperative trajectory. These patients could be offered supervised prehabilitation for surgery, a preoperative geriatric assessment to obtain a holistic view of the patient or more frequent follow-up visits with their own oncologist or surgeon to motivate them and their caregivers for surgery.

Furthermore, stratification of patients by risk of postoperative complications for intervention trials may improve the effects of the interventions under investigation – such as Enhanced Recovery After Surgery (ERAS) programs[73] or ischemic conditioning to increase perfusion of the gastric tube[74]. As an example, the identification of generalized arterial calcification as a risk factor for anastomotic leakage in chapter 11 forms the basis of the recently initiated

14

multicenter phase-II intervention trial evaluating the safety and feasibility of laparoscopic ischemic conditioning of the gastric tube prior to transthoracic esophagectomy in patients with major arterial calcifications (ISCON-trial, ClinicalTrials.gov Identifier NCT03896399).

Lastly, as neoadjuvant therapy can induce high degrees of tumor regression, current non-surgical patients (due to advanced local tumor characteristics) may become new surgical candidates.[75] It has been reported feasible and beneficial in terms of survival to perform a radical resection combined with off-pump descending aorta replacement and adjuvant chemotherapy in 47 patients with a T4b esophageal tumor invading the aorta.[76] Also, there is evidence that patients with cT4b tumors can be safely treated with robot-assisted minimally invasive esophagectomy after long-course chemoradiotherapy with a radical resection rate of 90%.[75]

Final remarks

The research presented in this thesis contributes to a more nuanced decision-making for esophageal cancer patients. Over the last years, personalized medicine has become a popular word in medical (cancer) research. We aim to differentiate treatment strategies per patient, but will inevitably be limited by studies that analyze outcomes on a group level – even though we are provided with more detailed patient and tumor genomic information using big data. The risk stratified selection of treatment as described before in this chapter is one example of an approach to research outcomes of specific treatments in smaller subgroups of patients. But above all, we – as physicians – should remember that the incorporation of the preferences of our patients in treatment decision making is the only way to truly deliver personalized medicine.

Conclusions

Part I. Neoadjuvant chemoradiotherapy
- Physical functioning deteriorates and fatigue increases in esophageal cancer patients who underwent neoadjuvant chemoradiotherapy. The occurrence of adverse events during neoadjuvant chemoradiotherapy is associated with a sharper impairment of health-related quality of life and esophageal cancer-specific symptoms (chapter 2).
- Esophageal tumor motion during radiation treatment is highly variable between and within patients with esophageal cancer (chapter 3).
- A higher total neoadjuvant radiation dose increases pathologic response in terms of pathologic major response, but does not impact pathologic complete response rates in esophageal cancer patients (chapter 4).

Part II. Treatment response assessment
- Changes on ^{18}F-FDG PET/CT after neoadjuvant chemoradiotherapy and early changes on DW-MRI during neoadjuvant chemoradiotherapy can help identify pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer and might be of complementary value in the assessment of pathologic complete response (chapter 5).
- The relative change in tumor cellularity as measured on DW-MRI during the first 2 weeks of neoadjuvant chemoradiotherapy is the most predictive for pathologic complete response in esophageal cancer patients compared to the other weeks of neoadjuvant chemoradiotherapy (chapter 6).
- A multi-center observational trial will develop a model that predicts the probability of pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer, based on DW-MRI, DCE-MRI and ^{18}F-FDG PET/CT (PRIDE study, chapter 7).
- Repeated imaging with both MRI and ^{18}F-FDG PET/CT is generally well tolerated by patients for the assessment of response to neoadjuvant chemoradiotherapy for esophageal cancer (chapter 8).

14

Part III. Surgical treatment
- Surgical treatment of esophageal cancer in the era of multimodality management focuses on the selection of patients who will benefit from surgery, based on their physical status and response to neoadjuvant therapy, as well as optimization of the entire perioperative trajectory (chapter 9).
- One in 7 patients who started neoadjuvant chemoradiotherapy for esophageal cancer do not proceed to surgical resection and have a decreased one-year overall survival compared to patients who do proceed to surgical resection (chapter 10).

- Calcification of the coronary and supra-aortic arteries as measured on preoperative diagnostic CT scans are predictive of cervical anastomotic leakage after esophagectomy, suggesting that generalized cardiovascular disease is a strong indicator for the risk of leakage (chapter 11).
- Acute surgical interventions for esophageal and gastric cancer are rare. Minimally invasive surgery for gastric cancer is safe and feasible in the acute setting, with at least comparable postoperative clinical and short-term oncological outcomes compared to open surgery (chapter 12).

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14

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14

APPENDICES

Summary in Dutch
(Nederlandse samenvatting)

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List of publications

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(Dankwoord)

Curriculum Vitae

Summary in Dutch (Nederlandse samenvatting)

Inleiding

Slokdarmkanker is wereldwijd de zevende meest voorkomende vorm van kanker. Jaarlijks worden er bijna 600.000 patiënten met slokdarmkanker gediagnosticeerd, waarvan 2.500 in Nederland. In totaal komt 60% van deze patiënten in aanmerking voor een in opzet curatieve behandeling, die tegenwoordig bestaat uit chemotherapie en bestraling (de zogeheten neoadjuvante chemoradiotherapie) gevolgd door een slokdarmresectie. Het doel van neoadjuvante chemoradiotherapie is het verkleinen van de tumor, waardoor de kansen op een radicale resectie en overleving worden vergroot. Door de toevoeging van neoadjuvante chemoradiotherapie aan de behandeling is de vijfjaarsoverleving van patiënten gestegen van 33% naar 47%. Echter, dit betekent dat nog steeds de helft van de patiënten met slokdarmkanker zonder uitzaaiingen naar andere organen is overleden vijf jaar na de behandeling. Dit komt onder andere doordat niet elk onderdeel van de behandeling bij iedere patiënt even effectief is, bovendien de behandeling gepaard gaat met het risico op complicaties en tevens slokdarmkanker regelmatig recidiveert.

Uiteindelijk is het doel om iedere patiënt de optimale behandeling te geven, waarbij een zorgvuldige afweging van de voor- en nadelen hiervan centraal staat. In dat kader valt de afgelopen jaren veelvuldig de term *personalized medicine* wanneer er gesproken wordt over behandelstrategieën tegen kanker. Dit idee staat momenteel nog ver van de hedendaagse klinische praktijk, met name doordat het individuele behandelingseffect nog onvoldoende voorspeld kan worden om patiënten een behandeling op maat aan te kunnen bieden. Het doel van het onderzoek beschreven in dit proefschrift is om de verschillende onderdelen van de behandeling van slokdarmkanker te optimaliseren. In **deel 1** wordt de neoadjuvante chemoradiotherapie behandeld, in **deel 2** het voorspellen van het effect van neoadjuvante chemoradiotherapie en in **deel 3** de chirurgische behandeling.

Neoadjuvante chemoradiotherapie

Neoadjuvante chemoradiotherapie bestaat voor patiënten met slokdarmkanker in Nederland uit chemotherapie en bestraling gedurende vijf weken, waarna na zes tot tien weken een slokdarmresectie plaatsvindt. **Deel 1** verschaft inzicht in de mogelijkheden om de effectiviteit van de behandeling te optimaliseren en bijwerkingen te minimaliseren.

Het effect van neoadjuvante chemoradiotherapie en complicaties daarvan op de kwaliteit van leven van patiënten met slokdarmkanker wordt beschreven in **hoofdstuk 2**. Patiënten werden gevraagd om voor en na de behandeling met neoadjuvante chemoradiotherapie een vragenlijst in te vullen over hun kwaliteit van leven. Neoadjuvante chemoradiotherapie blijkt een negatief effect te hebben op het fysiek functioneren en de vermoeidheid, terwijl patiënten aan de andere kant minder last krijgen van pijn bij het slikken. Patiënten die

complicaties ondervonden van de behandeling hadden één maand na de behandeling meer pijn, verlies van smaak en meer problemen met eten, vergeleken met patiënten zonder complicaties. Bovendien blijkt angst een veel voorkomend symptoom bij patiënten met slokdarmkanker, zowel voor als na de behandeling. Deze bevindingen benadrukken het belang om patiënten te informeren over de gevolgen van de behandeling op de kwaliteit van leven. Ook de kwaliteit van leven – en niet alleen de overleving – dient dus als uitkomst te gebruikt te worden in verder onderzoek naar behandelingen van slokdarmkanker.

Eén van de mogelijkheden om de bijwerkingen van neoadjuvante chemoradiotherapie te verminderen is een zeer precieze bestraling van de tumor, waardoor omliggend gezond weefsel wordt gespaard. Hiervoor kan gebruik worden gemaakt van beeldgestuurde bestraling en gepersonaliseerde bestralingsmarges (Figuur 1). **Hoofdstuk 3** beschrijft als een eerste stap de variatie tussen patiënten in de beweging van de slokdarmtumor tijdens de bestraling. In deze studie ondergingen patiënten die werden behandeld met neoadjuvante chemoradiotherapie zes MRI scans. Tijdens deze cine-MRI scan worden er 75 scans binnen 45 seconden gemaakt, waardoor de beweging van de slokdarm kan worden onderzocht. De beweging van de slokdarmtumor vindt voornamelijk plaats in de craniocaudale (verticale) richting, veroorzaakt door de ademhaling. Daarnaast zijn er grote verschillen in de beweging van de slokdarmtumor binnen één patiënt en tussen verschillende patiënten. Het is dus noodzakelijk om niet alleen voorafgaand aan de bestraling de beweging van de slokdarmtumor vast te stellen, maar ook gedurende het traject van de neoadjuvante chemoradiotherapie.
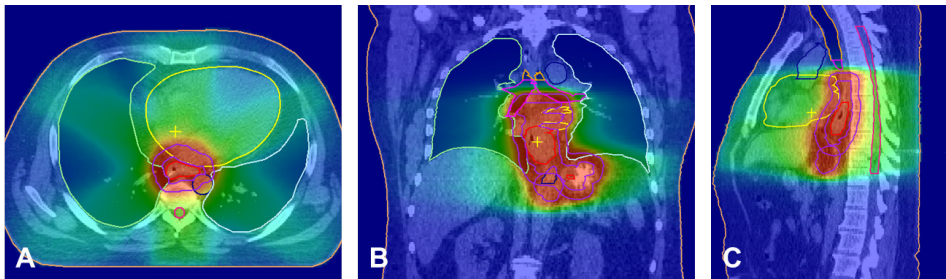
Figuur 1. Een voorbeeld van een bestralingsplan van een patiënt met slokdarmkanker waarin de dosis straling als een kleurenspectrum zichtbaar is. De slokdarmtumor is rood omlijnd en de onzekerheidsmarges voor de bestraling zijn paars omlijnd (*A* transversaal aanzicht, *B* coronaal aanzicht, *C* sagittaal aanzicht).

Behalve gepersonaliseerde bestralingsmarges, maakt beeldgestuurde bestraling het ook mogelijk om de bestralingsdosis te laten variëren binnen verschillende delen van de tumor (*dose painting*). **Hoofdstuk 4** beantwoordt de vraag of een behandeling met een hogere neoadjuvante bestralingsdosis resulteert in een beter effect van de behandeling op de slokdarmtumor. Behandelstrategieën uit Nederland, België en de Verenigde Staten zijn met elkaar vergeleken. Hieruit blijkt dat er geen sprake is van een overtuigende dosis-respons relatie voor slokdarmkanker.

**Het voorspellen van het behandelingseffect**
Het effect van neoadjuvante chemoradiotherapie is niet bij iedere patiënt hetzelfde. Er is sprake van een pathologisch complete respons wanneer het effect van de neoadjuvante chemoradiotherapie zo goed is, dat er geen kankercellen meer worden gevonden in het slokdarmpreparaat bij microscopisch onderzoek na de slokdarmresectie. Bij ongeveer 30% van de patiënten is dat het geval en deze patiënten hebben de beste prognose. Een nauwkeurige voorspelling van een pathologisch complete respons zou onderzoekers in staat stellen om de haalbaarheid en uitkomsten van een orgaansparende behandelstrategie – waarbij een slokdarmresectie achterwege gelaten wordt – te onderzoeken.

Er is ook een groep patiënten waarbij er vrijwel geen effect meetbaar is van de neoadjuvante chemoradiotherapie (non-respons), terwijl de behandeling wel gepaard gaat met het risico op bijwerkingen. Deze patiënten zouden onder andere baat kunnen hebben bij een nieuwe vorm van neoadjuvante therapie. Er bestaat dus voldoende reden om de keuze voor neoadjuvante chemoradiotherapie en/of de noodzaak voor een slokdarmresectie af te stemmen op de individuele patiënt.

Het voorspellen van het effect van neoadjuvante chemoradiotherapie met behulp van beeldvormende technieken zoals *positron emission tomography/computed tomography* (PET/CT) en *diffusion weighted magnetic resonance imaging* (DW-MRI) wordt besproken in **deel 2**. Beide technieken betreffen functionele beeldvormende technieken; dat wil zeggen dat ze niet alleen informatie verschaffen over de anatomie maar ook over de functie van het weefsel of het orgaan. PET/CT maakt gebruikt van radioactief gelabeld glucose die zich concentreert in weefsels met een verhoogd metabolisme, zoals kankercellen of een ontsteking (Figuur 2). DW-MRI berust op de beweeglijkheid van watermoleculen als een marker voor celdichtheid binnen een weefsel. Over het algemeen is de celdichtheid van een tumor groter dan van het omliggende weefsel en zal de celdichtheid afnemen als de behandeling met chemoradiotherapie effectief is en kankercellen afsterven (Figuur 3).
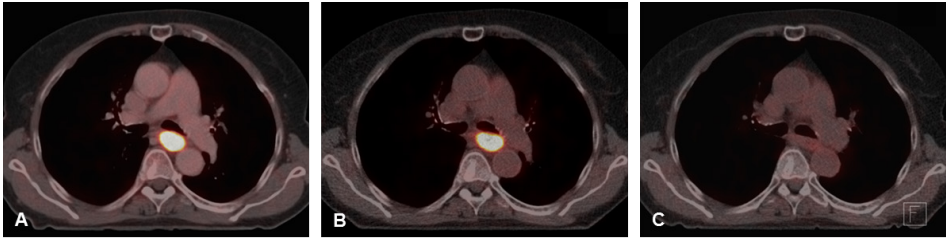
Figuur 2. Transversale weergaves van een PET/CT scan van een patiënt met slokdarmkanker voor (*A*), tijdens (*B*) en na (*C*) de behandeling met neoadjuvante chemoradiotherapie. Er is een duidelijke afname zichtbaar van het signaal ter plaatse van de slokdarmtumor na de neoadjuvante chemoradiotherapie (*C*).
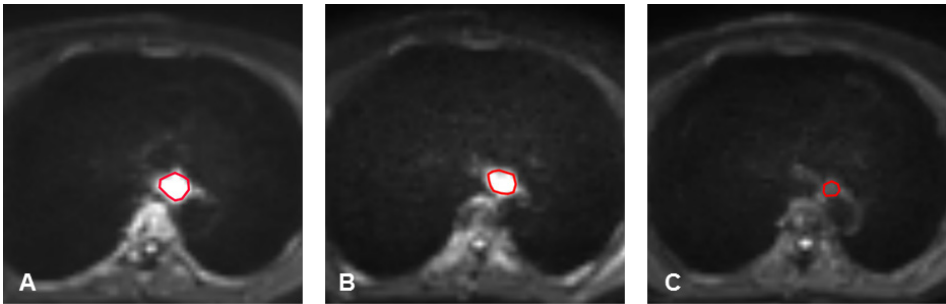
Figuur 3. Transversale weergaves van een DW-MRI scan van een patiënt met slokdarmkanker voor (*A*), tijdens (*B*) en na (*C*) de behandeling met neoadjuvante chemoradiotherapie. Het versterkte signaal op de scan binnen de rode omlijning die de slokdarmtumor betreft wijst op een hoge celdichtheid en neemt af naarmate de behandeling vordert.

De afzonderlijke en gecombineerde waarde van PET/CT en DW-MRI voor het voorspellen van het effect van neoadjuvante chemoradiotherapie bij patiënten met slokdarmkanker wordt beschreven in **hoofdstuk 5**. Dit onderzoek is het resultaat van een samenwerking tussen het Universitair Medisch Centrum Utrecht, het Antoni van Leeuwenhoek Ziekenhuis in Amsterdam en het MD Anderson Cancer Center in Houston. Patiënten die deelnamen aan het onderzoek ondergingen een PET/CT scan en MRI scan voor, tijdens en na de neoadjuvante chemoradiotherapie. Veranderingen op de PET/CT scan na afloop van de neoadjuvante chemoradiotherapie bleken het meest nuttig voor het voorspellen van een pathologisch complete respons. Voor DW-MRI zijn dat de veranderingen op de scan tijdens de neoadjuvante chemoradiotherapie. Ook zijn PET/CT en DW-MRI mogelijk van toegevoegde waarde voor het voorspellen van een pathologisch complete respons. Met behulp van een model waarin de bevindingen van de PET/CT scans en DW-MRI scans werden gecombineerd, kon met 83% zekerheid worden vastgesteld welke patiënten een pathologisch complete respons hadden.

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Hoofdstuk 6 borduurt voort op bovenstaande bevindingen, namelijk door het optimale moment voor de DW-MRI scan te onderzoeken tijdens neoadjuvante chemoradiotherapie om het effect van de behandeling zo accuraat mogelijk te kunnen voorspellen. In deze prospectieve studie hebben patiënten tijdens de neoadjuvante chemoradiotherapie wekelijks een DW-MRI scan ondergaan. De verandering in signaal op DW-MRI scans gedurende de eerste twee weken van neoadjuvante chemoradiotherapie is uitermate veelbelovend voor het voorspellen van een pathologisch complete respons. Deze informatie wordt nu gebruikt om de belasting van patiënten te minimaliseren in de multicenter MRI validatiestudie, waarvan de achtergrond en het protocol worden beschreven in **hoofdstuk 7**. In deze studie wordt op basis van gegevens van PET/CT scans, MRI scans en circulerend tumor DNA (ctDNA) een model ontwikkelt waarmee het effect van neoadjuvante chemoradiotherapie op de tumor accuraat voorspeld kan worden. Dit model heeft als doel om in de toekomst slokdarmresecties veilig achterwege te laten bij patiënten met een hoge kans op een pathologisch complete respons na de behandeling met chemoradiotherapie. De zeer intensieve behandeling van slokdarmkanker zou daardoor beter afgestemd kunnen worden op de individuele patiënt met zijn of haar wensen.

Het tweede onderdeel van het proefschrift wordt afgesloten door **hoofdstuk 8**. Hierin wordt de fysieke en de mentale belasting van extra PET/CT scans en MRI scans gedurende de neoadjuvante chemoradiotherapie voor patiënten geëvalueerd met behulp van vragenlijsten. Het blijkt dat patiënten deze extra onderzoeken over het algemeen goed verdragen en dat zij weinig last hebben van pijn, angst, schaamte en ongemak. Patiënten geven MRI scans de voorkeur boven PET/CT scans. Zowel PET/CT en MRI scans worden vanuit het oogpunt van de patiënt goed verdragen en kunnen beide worden gebruikt voor respons evaluatie.

Chirurgische behandeling
De slokdarmresectie is een tot op heden essentieel onderdeel van de curatieve behandeling van patiënten met slokdarmkanker. Bij een slokdarmresectie wordt de continuïteit van het spijsverteringskanaal veelal hersteld door de maag door het middenrif richting de borstkas te mobiliseren en daar of in de hals te verbinden met het resterende deel van de slokdarm. Hierdoor wordt er een buismaag gecreëerd. Door de ligging van de slokdarm dichtbij het hart, de longen en de aorta is het een gecompliceerde procedure met een relatief hoog risico op complicaties en zelfs overlijden.

De onderzoeken beschreven in **deel 3** van dit proefschrift zijn alle gericht op de rol van de chirurgische behandeling van slokdarmkanker in een tijd waarin verschillende behandelingen – zoals chemotherapie, radiotherapie en chirurgie – worden gecombineerd.

In **hoofdstuk 9** wordt de beschikbare literatuur over de rol van de chirurgische behandeling van slokdarmkanker uiteengezet. Uit deze review wordt duidelijk dat het van groot belang is om de juiste patiënten te selecteren voor een slokdarmresectie. Belangrijke factoren die hierbij een rol spelen, zijn de aanwezigheid van comorbiditeit, fysieke gesteldheid en de mate van respons op neoadjuvante therapie. Daarnaast wordt het perioperatieve traject voor patiënten de laatste jaren geïntensiveerd door de samenwerking met fysiotherapeuten, diëtisten en pijnspecialisten. Uiteraard hebben al deze ontwikkelingen als doel om de prognose van patiënten met slokdarmkanker te verbeteren.

Ondanks dat de voordelen van neoadjuvante chemoradiotherapie onomstotelijk zijn vastgesteld, is de behandeling geassocieerd met bijwerkingen. Dit is met name relevant wanneer deze bijwerkingen voorkomen dat de patiënt vervolgens een slokdarmresectie kan ondergaan. Door middel van een landelijke studie met data van de jaren 2015 en 2016, wordt in **hoofdstuk 10** aangetoond dat maar liefst één op de zeven patiënten die starten met neoadjuvante chemoradiotherapie geen slokdarmresectie ondergaat. Deze patiënten hebben een slechtere overlevingskans dan patiënten die wel een slokdarmresectie ondergaan. Deze bevindingen kunnen als uitgangspunt fungeren voor toekomstig onderzoek, waarin onderzocht zou moeten worden of deze patiëntengroep kan worden geselecteerd voorafgaand aan de behandeling. Ook de centralisatie van oncologische zorg en een betere begeleiding zouden mogelijk kunnen leiden tot meer patiënten die een slokdarmresectie ondergaan.

Om postoperatieve complicaties met ernstige gevolgen te kunnen voorkomen of voortijdig te kunnen herkennen, is het belangrijk om inzicht te krijgen in risicofactoren voor het ontstaan van complicaties. Een gevreesde complicatie na een slokdarmresectie betreft lekkage van de verbinding tussen de buismaag en het resterende deel van de slokdarm (naadlekkage). Onze onderzoeksgroep heeft eerder onder andere aangetoond dat atherosclerose van de thoracale aorta geassocieerd is met het ontstaan van naadlekkage. **Hoofdstuk 11** beschrijft of deze associatie gebaseerd is op problemen in de directe bloedvoorziening van de buismaag, of dat het een gegeneraliseerd vasculair probleem betreft. Aangetoond is dat calcificaties van de supra-aortale en coronaire arteriën voorspellend zijn voor naadlekkage na een slokdarmresectie. Hieruit kan worden geconcludeerd dat het inderdaad een gegeneraliseerd vasculair probleem betreft. Deze risicofactor kan worden meegenomen in prognostische modellen die individuele risico's op postoperatieve complicaties inschatten in de toekomst.

Tot slot is de toepassing van minimaal invasieve chirurgie een mogelijkheid om postoperatieve complicaties te verminderen. In de electieve setting wordt dit al veelvuldig

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toegepast voor slokdarmkanker. Echter, er is weinig bekend over de toepassing van minimaal invasieve chirurgie in de acute setting. Het beschreven onderzoek in **hoofdstuk 12** toont met behulp van een landelijk cohort aan dat acute slokdarmresecties zeldzaam zijn. Daardoor konden complicaties van minimaal invasieve chirurgie en open chirurgie in de acute setting niet met elkaar worden vergeleken. Voor maagkanker daarentegen lijkt de toepassing van minimaal invasieve chirurgie in de acute setting veilig op het gebied van postoperatieve complicaties en oncologische resultaten.

Conclusie

Ondanks dat er alleen al in het afgelopen jaar meer dan 2.000 publicaties zijn verschenen over slokdarmkanker, is er nog veel onbekend op het gebied van de etiologie, prognose en behandeling van patiënten met slokdarmkanker. Om de prognose van slokdarmkankerpatiënten daadwerkelijk te kunnen verbeteren, is het van groot belang om onderzoek te doen waarvan de resultaten leiden tot veranderingen in de klinische praktijk. De onderzoeken beschreven in dit proefschrift dragen hieraan bij door de verschillende vormen van neoadjuvante chemoradiotherapie en de gevolgen hiervan te bestuderen, bovendien te streven naar accurate evaluatie van respons van de tumor op neoadjuvante chemoradiotherapie en door de chirurgische behandeling te optimaliseren.

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List of publications

1. **Borggreve AS***, Goense L*, van Rossum PSN, et al. Preoperative prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal cancer using 18F-FDG PET/CT and DW-MRI: a prospective multicenter study. *Int J Radiat Oncol Biol Phys*. 2020. [Epub ahead of print]

2. **Borggreve AS***, den Boer RB*, van Boxel GI, et al. The Predictive Value of Low Muscle Mass as Measured on CT Scans for Postoperative Complications and Mortality in Gastric Cancer Patients: A Systematic Review and Meta-Analysis. *J Clin Med*. 2020;9(1):199.

3. **Borggreve AS**, Heethuis SE, Boekhoff MR, et al. Optimal timing for prediction of pathologic complete response to neoadjuvant chemoradiotherapy with diffusion-weighted MRI in patients with esophageal cancer. *Eur Radiol*. 2019. [Epub ahead of print]

4. Thomas M*, **Borggreve AS***, van Rossum PSN, et al. Radiation dose and pathological response in oesophageal cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery: a multi-institutional analysis. *Acta Oncol*. 2019;58(10):1358-1365.

5. Seesing MFJ, **Borggreve AS**, Ruurda JP, van Hillegersberg R. New-onset atrial fibrillation after esophagectomy for cancer. *J Thorac Dis*. 2019;11(Suppl 5):S831-S834.

6. **Borggreve AS**, van Rossum PSN, Mook S, et al. Frequency of surgical resection after starting neoadjuvant chemoradiotherapy in patients with esophageal cancer: A population-based cohort study. *Eur J Surg Oncol*. 2019;45(10):1919-1925.

7. **Borggreve AS**, Goense L, Brenkman HJF, et al. Imaging strategies in the management of gastric cancer: current role and future potential of MRI. *Br J Radiol*. 2019;92(1097):20181044.

8. **Borggreve AS**, Mook S, Verheij M, et al. Preoperative image-guided identification of response to neoadjuvant chemoradiotherapy in esophageal cancer (PRIDE): a multicenter observational study.
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9. Plate JDJ*, **Borggreve AS***, van Hillegersberg R, Peelen LM. Post Hoc Power Calculation: Observing the Expected. *Ann Surg*. 2019;269(1):e11.

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11. Heethuis SE, Goense L, van Rossum PSN, **Borggreve AS**, et al. DW-MRI and DCE-MRI are of complementary value in predicting pathologic response to neoadjuvant chemoradiotherapy for esophageal cancer. *Acta Oncol. 2018*;57(9):1201-1208.

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13. Goense L, Meziani J, **Borggreve AS**, et al. Role of adjuvant chemoradiotherapy after endoscopic treatment of early-stage esophageal cancer: a systematic review. *Minerva Chir*. 2018;73(4):428-436.

14. Seesing MFJ, Scheijmans JCG, **Borggreve AS**, et al. The predictive value of new-onset atrial fibrillation on postoperative morbidity after esophagectomy. *Dis Esophagus*. 2018;31(11).

15. Goense L, **Borggreve AS**, Heethuis SE, et al. Patient perspectives on repeated MRI and PET/CT examinations during neoadjuvant treatment of esophageal cancer. *Br J Radiol*. 2018;91(1086):20170710.

16. **Borggreve AS**, Goense L, van Rossum PSN, et al. Generalized cardiovascular disease on a preoperative CT scan is predictive for anastomotic leakage after esophagectomy. *Eur J Surg Oncol*. 2018;44(5):587-593.

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18. Lam MG, **Borggreve AS**, Landman AJ, et al. Accessory Left Gastric Artery from Left Hepatic Artery is a Potential Risk for Radioembolization Complications. *Cardiovasc Intervent Radiol*. 2016;39(9):1367-8.

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Acknowledgements (Dankwoord)

De afgelopen jaren heb ik het voorrecht gehad om samen te werken met veel inspirerende mensen. Ik heb met volle teugen genoten van mijn tijd als arts-onderzoeker en er samen met jullie alles uit gehaald wat er in zat – niet in de laatste plaats buiten het ziekenhuis. Dit proefschrift is tot stand gekomen mede dankzij de directe en indirecte bijdrage van velen. De onderstaande personen wil ik graag in het bijzonder bedanken.

In de eerste plaats **de patiënten met slokdarmkanker** die geheel belangeloos hebben deelgenomen aan de onderzoeken beschreven in dit proefschrift in een periode die van hen en hun naasten sowieso al het uiterste vraagt. Het is bewonderenswaardig dat jullie als reden voor deelname aan onderzoek slechts de hoop uitspraken dat de behandeling en prognose van patiënten met slokdarmkanker ná jullie beter zou worden. Ik hoop dan ook dat het onderzoek beschreven in dit proefschrift daar op enige manier aan zal bijdragen.

Prof. dr. van Hillegersberg, beste Richard, je kritische blik, humor, vertrouwen en vermogen altijd twee stappen vooruit te denken creëren een omgeving waarin iedereen wordt gestimuleerd het beste uit zichzelf te halen. Ik ben dankbaar voor de ontwikkelingen die ik de afgelopen jaren onder jouw begeleiding heb mogen doormaken van student onderzoeker tot doctor. Het podium en de vrijheid die je aan je onderzoekers geeft waardeer ik enorm. Met veel plezier maak ik deel uit van je fantastische onderzoeksgroep!

Prof. dr. Terhaard, beste Chris, ik ben je erg dankbaar voor de kansen en de ruimte die jij en de afdeling mij hebben geboden gedurende mijn promotietraject. Bovendien waren je overkoepelende blik en de achtergrondinformatie die je verschafte over veel onderwerpen tijdens mijn voortgangsbesprekingen erg waardevol voor ons onderzoek.

Prof. dr. Ruurda, beste Jelle, toen ik in 2014 een email stuurde dat ik als student onderzoek wilde gaan doen, kreeg ik meteen een enthousiast en uitnodigend bericht terug. Datzelfde enthousiasme, je gevoel voor humor en je toegankelijkheid hebben onderzoek doen de afgelopen jaren leuk gemaakt! Heel veel dank bovendien voor jouw eerlijkheid, pragmatische instelling en altijd snelle reacties. Jij weet overal mogelijkheden te zien en te creëren, en de toewijding waarmee je de kliniek met de wetenschap weet te combineren is een voorbeeld.

Dr. van Rossum, beste Peter, je gedetailleerde revisies op manuscripten en je uitgebreide kennis over de literatuur op het gebied van slokdarmkanker hebben het onderzoek beschreven in dit proefschrift naar een hoger plan gebracht. Bedankt ook voor je kritische vragen die mij vaak uitdaagden om verder te denken!

Leden van de beoordelingscommissie, **prof. dr. P.A. de Jong, prof. dr. ir. J.J.W. Lagendijk, prof. dr. M.R. Vriens, prof. dr. J.J.B. van Lanschot en prof. dr. M. Verheij**, hartelijk dank voor jullie interesse en de tijd die jullie hebben genomen om mijn proefschrift te beoordelen. Ik heb met veel plezier met jullie samengewerkt gedurende verschillende onderdelen van mijn promotie en ik kijk er naar uit om met jullie van gedachten te wisselen over de inhoud van mijn proefschrift.

Collega's van de oesmaag-onderzoeksgroep, **Hylke Brenkman, Gijs van Boxel, Ingmar Defize, Emma Gertsen, Lucas Goense, Sylvia van der Horst, Feike Kingma, Kevin Parry, Bernadette Schurink, Maarten Seesing, Pieter van der Sluis, Arjen van der Veen, Roy Verhage, Els Visser en Teus Weijs**, eendracht maakt macht! Ik had me geen leukere, meer inspirerende of meer betrokken onderzoeksgroep kunnen wensen. Het is een voorrecht om onderzoek te mogen doen met collega's waarvan je weet dat ze altijd voor je klaar staan, of dat nou tijdens de researchmeeting, op congressen, in de kelder of aan de bar is! **Lucas**, wat heb ik veel geleerd, maar vooral ook veel gelachen met jou als kamergenoot! Bedankt voor je eerlijke adviezen en de eindeloze gesprekken die we hebben gevoerd over de (on)zin van de wetenschap en het leven. **Feike**, tegelijkertijd gestart met onze promotietrajecten en sindsdien altijd slechts *one call away*. Jouw goede humeur en eerlijke humor, als ook jouw behulpzaamheid en bereidheid mee te denken met bijna elk onderdeel in dit proefschrift hebben er voor gezorgd dat wij vele uren met elkaar hebben doorgebracht. Wat mooi dat je vandaag naast me staat als paranimf!

Oesophagus-MRI onderzoekers, **Gert Meijer, Stella Mook, Sophie Heethuis, Sophie de Mol van Otterloo, Mick Boekhoff en Astrid van Lier**, bedankt voor jullie samenwerking en suggesties die onze onderzoekslijn vorm hebben gegeven. **Gert**, jouw laagdrempeligheid en oog voor detail maken je een unieke onderzoeker van wie ik veel heb kunnen leren. **Stella**, jouw kennis is mijn onderzoek op vele manieren ten goede gekomen, bedankt voor je betrokkenheid en fantastische gevoel voor humor. **Sophie**, zonder jou was ik nu nog steeds scans aan het intekenen – bedankt voor al je scripts en uitleg over MRI scans.

Arts-onderzoekers, arts-assistenten en stafleden van de heelkunde uit het UMC Utrecht, hartelijk dank voor alle inspirerende en onvergetelijke wetenschapsdagen, congressen, skireizen, borrels en weekenden. Het was altijd weer schitterend en ik ben blij dat ik weer in jullie midden ben!

Arts-onderzoekers van de afdeling radiotherapie, bedankt voor jullie gezelligheid, behulpzaamheid, de journal clubs – extra leerzaam dankzij de toewijding van **prof. dr. Lenny Verkooijen** –, lunches, weekstarts en het luisterend oor. In het bijzonder wil ik **mijn**

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kamergenoten – Lucas Goense, Sofie Gernaat, Jeanine Vasmel en Bart Pielkenrood – en mijn buren op de Q2 gang bedanken: door jullie ben ik geen dag met tegenzin naar mijn werk gegaan! **Sofie**, de manier waarop jij in het leven staat is voor mij enorm inspirerend, bedankt!

Dames van het secretariaat van de heelkunde – Romy, Marielle en Fatiha –, het secretariaat van de radiotherapie – Yvette, Judith en Leonie –, het afsprakenbureau en de (MRI) laboranten: jullie ondersteuning was onmisbaar bij de totstandkoming van dit proefschrift, bedankt voor jullie inzet!

Dr. Roks, beste David, bedankt voor jouw interesse en advies gedurende dit promotietraject. Je betrokkenheid bij mijn carrière en alles daarbuiten sinds je begeleiding van mij als semi-arts in 2015 waardeer ik zeer!

Chirurgen en collega's uit het Academisch Ziekenhuis Paramaribo, met veel plezier heb ik mijn eerste maanden als arts-assistent bij jullie doorgebracht. Bedankt voor alles wat ik heb mogen doen en leren onder jullie supervisie en dat jullie me thuis hebben laten voelen! Ik hoop van harte dat we in de toekomst opnieuw samen zullen werken.

Lieve **vrienden, clubgenoten, oud-huisgenoten, studiegenoten, hockeyteamgenoten en Paramaribo-gang**, bedankt voor de ontelbare mooie momenten buiten het UMC de afgelopen jaren! Jullie loyaliteit, belangstelling en gezelligheid waardeer ik enorm. Op naar nog vele momenten samen! In het bijzonder wil ik graag **Eva Bindels, Sanne Bergmans, Tabitha Koops en Floor Sijbrandij** bedanken: jullie vriendschap is voor mij al meer dan 10 jaar onmisbaar en brengt me zo veel goeds! En *last but not least*, **Martine Hendriksma**, betrokken vanaf dag één van onze studie terwijl je plekken voor me bezet hield in de collegebanken, tot nu als paranimf. Bedankt voor de gesprekken over promoveren, je inspirerende doorzettingsvermogen, je vrolijkheid en natuurlijk je gezelligheid!

Lieve **Armanda en Juliette**, er is niets mooiers dan opgroeien met jullie als zussen! Vanaf mijn geboorte hebben jullie me bedolven onder liefde, gezelligheid, eerlijkheid en grappen. Dat jullie onvoorwaardelijk voor me klaar staan – in Utrecht, Den Haag, San Diego, op de piste, op de Kilimanjaro of waar dan ook – betekent heel veel voor me. Ik kijk uit naar de mooie momenten die ons de rest van ons leven nog te wachten staan! Lieve **Viren, Arth en Emile** – ik kan me geen betere *x-tended family* wensen en prijs me ontzettend gelukkig met jullie allen om me heen!

Lieve **papa en mama**, zonder jullie had ik dit proefschrift – zowel letterlijk als figuurlijk – nooit kunnen schrijven. Door jullie onvoorwaardelijke steun en liefde, grenzeloze vertrouwen en kritische blik hebben jullie mij het beste kompas gegeven om door het leven te navigeren en mijn dromen te verwezenlijken. De afgelopen jaren waren we vaak ver van elkaar verwijderd in geografische zin, maar dat jullie mijn grootste supporters zijn heb ik altijd geweten! Ik ben jullie oneindig dankbaar.

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Curriculum vitae auctoris

Alicia Sabine Borggreve was born on March 8, 1992 in Venray, the Netherlands. At the age of 9, Alicia moved to Waalre with her parents and 2 older sisters. After graduating (*cum laude*) from the Pleincollege Van Maerlant, Eindhoven, she started medical school at the University of Utrecht in 2009. During her studies, she was an active member of several student organizations and taught practical skills to undergraduate medical students. Furthermore, Alicia gained international experience during clinical internships at Tygerberg Hospital (Stellenbosch University, South Africa) and the University of California (San Diego, United States of America). In the final years of her studies, she developed a special interest in general surgery and started her first project on esophageal cancer as a student researcher in 2014.

After obtaining her medical degree in 2016, Alicia started as a PhD candidate focusing on multimodality treatment and response assessment in 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, prof. dr. J.P. Ruurda and dr. P.S.N. van Rossum. In parallel with her PhD program, she obtained a postgraduate Master of Science degree in Epidemiology at the University of Utrecht specializing in Clinical Epidemiology and Medical Statistics.

Alicia started her clinical career as a surgical resident not in training at the Department of Surgery at the Academic Hospital Paramaribo, Surinam in July 2019. In February 2020, she returned to the University Medical Center Utrecht as a surgical resident not in training. Alicia aspires to become a surgeon while maintaining her passion for research and health-care in low-resource settings.