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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

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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.

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 50 mg/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 had a M0 status. 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

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[a]	
	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/m^2 (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 [b]							
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%
Clinical T status [c]							
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 [c]							
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[d]	457	30.0%		82	38.1%	13	34.2%

BMI body mass index at diagnosis; *nCRT* neoadjuvant chemoradiotherapy; *WHO* World Health Organization.
[a] Please note: the patients who deceased during neoadjuvant chemoradiotherapy are also included in the patients who did not undergo surgical resection.
[b] Closely related comorbidities were considered as one category.
[c] Clinical T status and N status are based on AJCC TNM 7th edition.
[d] 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).

criteria of the CROSS trial based on one or a combination of the following characteristics: age ≥ 75 years (n = 211), cT4 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).

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.

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 Fig. 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%.

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.

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/m^2 (mean ± SD)	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 [a]				
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 [b]				
T1-T2	reference		reference	
T3-T4	1.50	0.87–2.68	1.21	0.85–1.72
Clinical N status [b]				
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[c]	1.17	0.71–1.91	0.99	0.70–1.40

BMI body mass index at diagnosis; *WHO* World Health Organization.
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.
[a] Closely related comorbidities were considered as one category.
[b] Clinical T status and N status are based on AJCC TNM 7th edition.
[c] 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 M0).

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

Reasons		(%)
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%

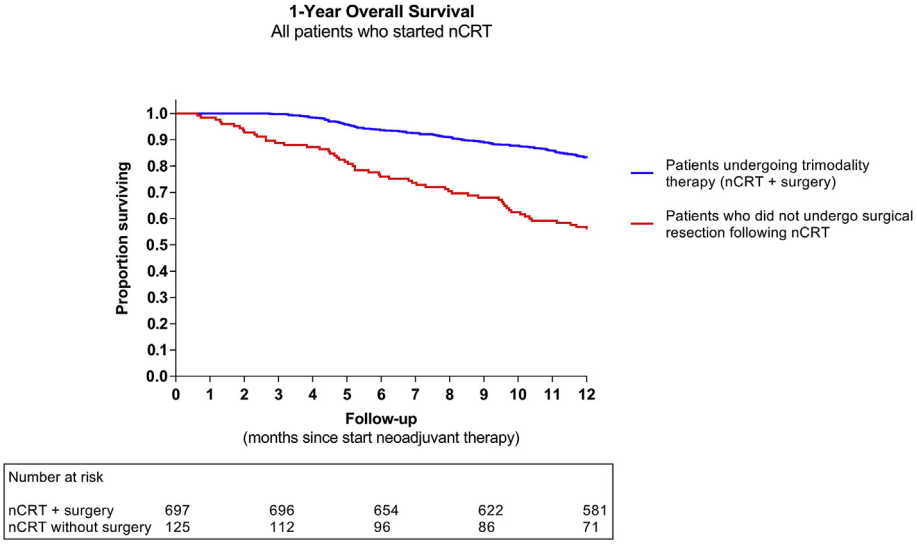

Fig. 1. Kaplan-Meier estimates of 1-year overall survival for patients with esophageal cancer that started neoadjuvant chemoradiotherapy (nCRT) in the Netherlands in 2015 and 2016. Please note that the categorization of patients by treatment, results in immortal time bias from the start of neoadjuvant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

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.

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 Fig. 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.

Conflict of interest statement

The authors have no conflicts of interest or financial ties to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.031.

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