The influence of treatment decisions on the outcome of esophageal cancer

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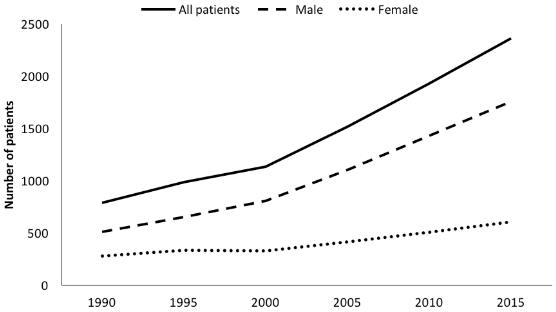
CHAPTER 1

Introduction

Introduction

Esophageal cancer is worldwide the eight most common type of cancer and the sixth leading cause of cancer related mortality[1]. The incidence of esophageal cancer in the Netherlands is rapidly rising with 789 patients diagnosed in 1990 to 2360 patients diagnosed in 2015 (Figure 1)[2].

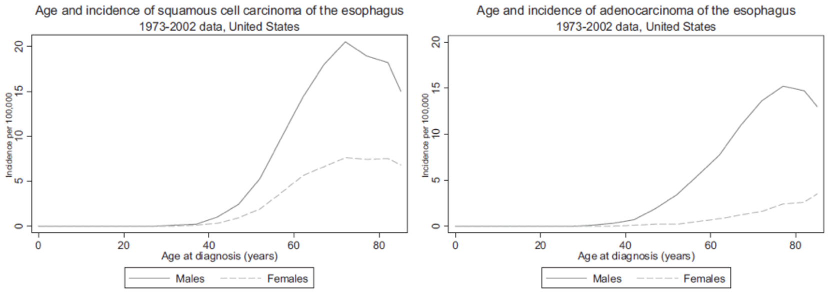
Figure 1. Incidence of esophageal cancer in the Netherlands (www.cijfersoverkanker.nl).



More than 90 percent of esophageal cancers are either squamous cell carcinomas or adenocarcinomas. The majority or the adenocarcinomas develop in the distal esophagus, whereas the squamous cell carcinomas most often develop in the middle and lower third[3]. In the development of squamous cell carcinoma of the esophagus, alcohol consumption and smoking are the most important risk factors. For adenocarcinoma of the esophagus, obesity, gastro-esophageal reflux disease (GERD) and Barrett's esophagus are the most important risk factors[3-5]. Esophageal cancer is mainly a disease of the elderly with most patients aged between 60 and 85 years at time of diagnosis (Figure 2)[4]. In the Netherlands approximately 30% of all diagnosed patients is 75 years or older[2].

The preferred treatment in non-metastatic resectable esophageal cancer in the Netherlands is a multidisciplinary approach with neoadjuvant chemoradiation followed by esophagectomy[6]. Esophageal cancer is unfortunately an aggressive disease with an early lymphatic and hematogenous dissemination. At diagnosis approximately 50% of the patients present with metastatic disease[7]. The overall 5-year survival of esophageal cancer is still poor ranging from 15% to 25% depending on stage and treatment[5].

Figure 2. Age and incidence of esophageal cancer by histological subtype
(SEER Stat Database: Incidence: SEER 9 Regs Public Use, November2004 submission, released April 2005).



Further research on esophageal cancer is important since it is an aggressive disease with a rapidly rising incidence, in which treatment requires a multidisciplinary approach in a challenging patient group with many elderly. This thesis will provide insight in important treatment decisions in **part 1** and will provide data on influence of neoadjuvant treatment in esophageal cancer in **part 2**.

Part 1. Treatment decisions in patients with esophageal cancer

The first successful resection of an esophageal tumor was described in 1877. A malignant stricture below the pharynx was treated with a local resection and a feeding esophagostomy was provided. Between 1877 and 1912 early esophageal surgical procedures were described, without any attempt to restore continuity. Between 1913 and 1938 the first attempts to restore continuity with a presternal tube of skin, stomach, jejenum or a rubber tube were performed. Ultimately, in 1938 the first successful transpleural esophageal resection with lymph node dissection and gastric tube reconstruction was described[8]. The modern era of esophageal surgery started after the second world war with more advanced anesthetic possibilities, anastomotic techniques, infection control and postoperative management[8]. In order to decrease the high postoperative morbidity and mortality after transthoracic esophagectomy, Orriger introduced the transhiatal esophagectomy without the need for a thoracotomy in 1978[9]. Nowadays, after further development and improvement of surgical techniques the esophagectomy has evolved to a complete minimally invasive transthoracic or transhiatal approach[10].

Throughout the years the outcome of esophageal cancer has further improved due to several factors, such as concentration of care, neoadjuvant treatment modalities, alternative treatment strategies, improved diagnostics and multidisciplinary decision making.

In order to further improve perioperative results, concentration of surgery has been proposed based on the results of studies by van Lanschot et al and Birkmeijer et al. showing a relation between hospital volume and postoperative mortality[11-13]. In the Netherlands concentration of care has evolved due to the introduction of minimum annual volume numbers and has been shown to improve outcome after esophageal surgery[11;14;15]. This concentration of care potentially leads to an improvement of surgical experience and perioperative care which is of crucial importance. The continuous refinements in the pre, intra- and postoperative management improve outcomes in esophageal cancer surgery. This has been shown in a high volume centre in which over more than two thousand transhiatal esophagectomies were performed. Postoperative mortality decreased from 4% to 1%, anastomotic leakage rate decreased from 14% to 9% and discharge within ten days increased from 52% to 78%[16].

In order to improve survival in patients with resectable esophageal cancer, perioperative strategies containing radiotherapy and/or chemotherapy were introduced. Perioperative radiotherapy and chemotherapy could improve local or systemic disease control by downstaging, eradicating micrometastatic disease and decrease further dissemination[17]. The first randomised controlled trials with perioperative radiotherapy, chemotherapy or chemoradiation were published in the nineties of the previous century[18]. Two important randomised controlled trials i.e. the CROSS[19] and MAGIC trial[20], revealed an impressive survival benefit of combining surgery with preoperative chemoradiation or perioperative chemotherapy respectively in patients with resectable esophageal or gastro-esophageal junction (GEJ) tumors. These results led to an increase in use of multimodality treatment, primarily neoadjuvant chemoradiation, in the Netherlands. Between 2000 and 2012 the use of multimodality treatment increased from 20% to 90% in esophageal cancer and from 6% to 85% in GEJ cancer[21].

Even though postoperative mortality decreased over time, esophageal cancer surgery remains high risk surgery with a relative high postoperative morbidity, especially in patients with multiple co-morbidities and a higher age[22-25]. Higher age is an important factor in 30-day postoperative mortality with a postoperative mortality of 10% in patients older than 75 years compared to postoperative mortality of 5% in patients younger than 65 years[26]. Elderly and vulnerable patients unfit for surgery are therefore often treated with alternative potentially curative modalities like definitive chemoradiation[5;27-30]. This different treatment strategy has an acceptable survival and is often well tolerated[28;29].

Hence, treatment of esophageal cancer has evolved to a complex patient tailored decisional process. In order to determine the best personalised approach for patients with esophageal cancer, all patients in the Netherlands need to be discussed at multidisciplinary team (MDT) meetings. These MDT meetings have shown their importance for rectal and breast cancer since it improves surgical outcomes through better patient management[31;32]. In esophageal cancer treatment it has shown to improve staging accuracy and often alterations in the initial treatment are made in almost one third of the cases[33;34].

Aim and outline of part 1.

In the current literature most studies have focussed on treatment results of patients who have actually received a potentially curative treatment in individual centres and not on the whole group of patients diagnosed with esophageal cancer, including those that have not received curative treatment. Several factors influence the decision to propose potentially curative treatment. Therefore, it is important to determine which factors influenced overall survival and whether these factors play a role in the decision to propose a potentially curative treatment. This decisional process will be investigated in **chapter one**. Furthermore, a large proportion of the patients with esophageal cancer are elderly patients. Unfortunately, most treatment strategies and guidelines are based on clinical trials in which elderly patients are often excluded. Therefore, it is of significant importance to investigate with real-world, population-based data the effect of different treatment options on survival in this specific group of patients. Treatment choices in this specific group will be addressed in **chapter two**. During local MDT meetings in the hospital of diagnosis in the Netherlands it is most often decided whether or not a patient is referred to an expert centre for further treatment. Hence, the hospital of diagnosis plays an important role in the probability of receiving potentially curative treatment. Two nationwide studies in gastric or pancreatic cancer have revealed the influence of hospital of diagnosis on the probability of undergoing curative treatment for gastric or pancreatic cancer[35;36]. The influence of hospital of diagnosis on the probability to receive curative treatment in esophageal cancer on a regional and nationwide scale will be studied in **chapter three** and **four**.

Part 2. The influence of neoadjuvant treatment on morbidity and oncological outcome in esophageal surgery

GEJ tumors are classified according to the Siewert classification[37] which had its epicentre within 5cm of the anatomic GEJ. The anatomic GEJ is defined as the proximal end of the gastric folds. Patients with resectable GEJ tumors are either treated via an esophagectomy followed by a gastric pull-up or by a gastrectomy with Roux-en-Y reconstruction. The literature does not provide conclusive evidence on the optimal surgical treatment strategy. Furthermore, GEJ tumors are both included in the two cornerstone randomised controlled trials (CROSS[19] and MAGIC[20]) which revealed impressive survival benefit of neoajuvant chemoradiation and perioperative chemotherapy. Again, the literature does not provide conclusive evidence on the optimal perioperative treatment strategy.

Since the introduction of neoadjuvant chemoradiation in esophageal cancer, the optimal timing of surgery after neoadjuvant treatment is unclear en needs to be elucidated. In clinical trials, the timing of surgery has been chosen empirically to be within 2 to 8 weeks after completion of neoadjuvant chemoradiation[38;39]. However, many factors such as toxicity of neoadjuvant chemoradiation, comorbidity, poor physical status and also logistical problems may postpone surgery beyond this timeframe. Postponing surgery might be beneficial since it could result in a better patient condition by the time of surgery and probably more tumor regression and higher complete response rates as shown in rectal cancer[40]. However it also raises the theoretic fears of primary or metastatic tumor growth and an increase in surgical complexity due to more radiation induced tissue damage and fibrosis.

Nowadays, esophageal surgery in the Netherlands has an acceptable low postoperative mortality, however still high rates of postoperative morbidity are described, especially pulmonary and anastomotic complications such as leakage and stenosis. Several factors, such as the presence of multiple co-morbidities, nutritional status, anastomotic location, anastomotic technique, and atherosclerotic vascular condition, are hypothesized to influence anastomotic leakage and stenosis[41-43]. Neoadjuvant chemoradiation might also play a role in developing anastomotic complications, however the literature shows conflicting results. Two meta-analyses revealed no difference in mortality and morbidity between patients receiving neoadjuvant chemoradiation and surgery and patients receiving surgery alone[44;45]. Furthermore, two randomized trials comparing neoadjuvant chemoradiation and surgery with surgery alone did not show a difference in morbidity and anastomotic complications between both groups[19;46]. In contrast, another study showed that the mean dose to the gastric fundus was a predictor for anastomotic leakage[47]. In addition, a recent study revealed that neoadjuvant chemoradiation had no influence on the incidence of postoperative complications, but only affected the severity of complications[48].

Aim and outline of part 2.

There is no conclusive evidence which perioperative regime (chemotherapy or chemoradiation) and which surgical resection (esophagectomy or gastrectomy) should be used in treatment of GEJ tumors since there are no specific trials performed in GEJ tumors and the two cornerstone perioperative trials (MAGIC and CROSS) both included GEJ tumors. Therefore, a study in a population- based setting that evaluates patterns of care in treatment strategies for GEJ tumors is of interest and could possibly elucidate part of this dilemma. Thus **Chapter Five** evaluates patterns of care in treatment strategies for GEJ tumors in a population-based setting.

In order to evaluate the influence of the time period between neoadjuvant chemoradiation and surgery on the postoperative morbidity, pathological response, and long-term survival, in **Chapter Six** a study was performed on the Catharina Hospital Eindhoven cohort to evaluate the influence of the time period between neoadjuvant chemoradiation and surgery on the postoperative morbidity, pathological response, and long-term survival. Since neoadjuvant chemoradiation is now standard of care and there several theoretical and practical concerns remain regarding a related possible increase in morbidity, we performed a study whether or not radiation dose to the fundus of the stomach influences postoperative anastomotic complications is needed. In **chapter seven** and **eight** the influence of radiation dose to the gastric fundus on postoperative anastomotic complications have been investigated in the Catharina Hospital Eindhoven and Amsterdam Academic Medical Center cohort.

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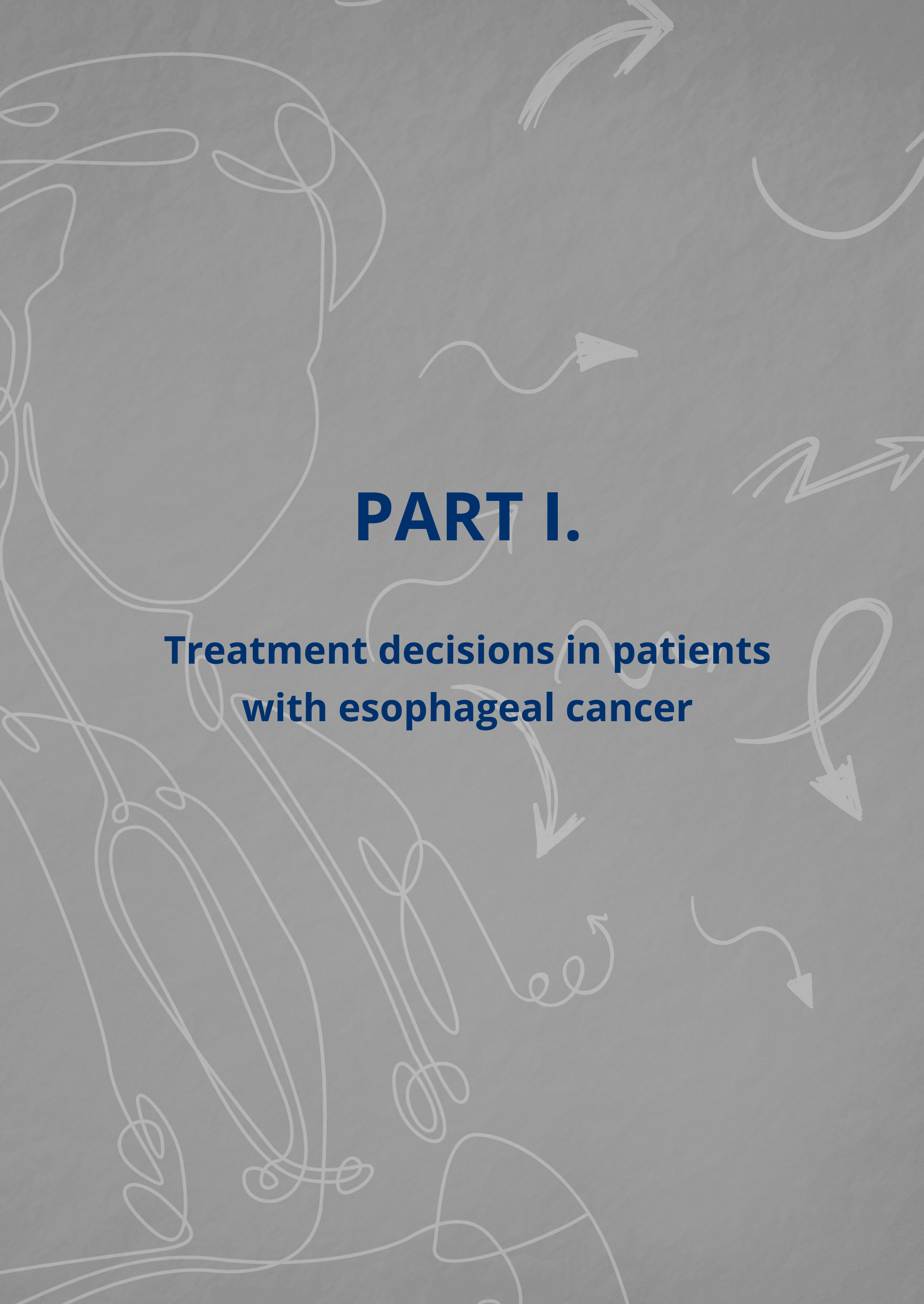


PART I.

Treatment decisions in patients with esophageal cancer

CHAPTER 2

Determinants in decision making for curative treatment and survival in patients with resectable esophageal cancer in the Netherlands: a population-based study

Authors:

M. Koëter MD[1]; L.N. van Steenbergen PhD[2]; V.E.P.P. Lemmens PhD[2,3]; H.J.T. Rutten MD, PhD[1,4]; J.A. Roukema MD, PhD[5]; G.A.P. Nieuwenhuijzen MD, PhD[1]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands

[2] Comprehensive Cancer Centre,
Eindhoven, The Netherlands

[3] Department of Public Health,
Erasmus University Medical Centre Rotterdam, The Netherlands

[4] Department of Surgery,
Maastricht University Medical Centre, The Netherlands

[5] Department of Surgery,
St. Elisabeth Hospital Tilburg, The Netherlands

Abstract

Background: Preferred treatment for resectable esophageal cancer is surgery with or without neoadjuvant treatment. However, esophageal surgery has high morbidity and in vulnerable patients with co-morbidity other treatment modalities can be proposed. We examined determinants in decision making for surgery and factors affecting survival in patients with resectable esophageal cancer in southern Netherlands.

Methods: All patients with resectable (T1-3, N0-1, M0-1A) esophageal cancer (n=849) diagnosed between 2003-2010 were selected from the population-based data of the Eindhoven Cancer Registry. Logistic regression analysis and multivariable Cox survival analysis were conducted to examine determinants of surgery and survival.

Results: Forty-five percent of the patients underwent surgery. In multivariable survival analysis only surgery, chemoradiation alone and tumor stage influenced Overall Survival (OS). Patients aged ≥70 years, a low socioeconomic status (SES), one or more co-morbidities, cT1-tumors, cN1-tumors, a squamous-cell carcinoma, and those with a proximal tumor were significantly less often offered surgical resection. Older patients and patients with cT1 tumors were less likely to receive chemoradiation alone. Patients with clinically positive lymph nodes or a proximal tumor were more likely to receive chemoradiation alone.

Conclusions: Treatment modalities including surgery and chemoradiation alone as well as stage of disease were independent predictors of a better OS in patients with potentially resectable esophageal cancer. Therefore, the decision to perform potentially curative treatment is of crucial importance to improve OS for patients with potentially resectable esophageal cancer. Although age and SES had no significant influence on overall survival, a higher age and low SES negatively influenced the probability to propose potentially curative treatment.

Introduction

Esophageal cancer is worldwide the eight most diagnosed type of cancer and it is the sixth leading cause of cancer deaths[1].The incidence of esophageal cancer in the Netherlands, especially adenocarcinoma, is rapidly rising from 1731 in 2000 to 2499 in 2010[2]. Esophageal cancer is an aggressive disease with early lymphatic and hematogenous dissemination, with a 5-year overall survival rate ranging between 15% and 51% depending on tumor stage and treatment[3-5]. At diagnosis, 50%-63% of the patients have in-situ or resectable esophageal cancer and are eligible for potentially curative endoscopic mucosal resection (EMR) or surgical treatment[6;7]. According to the Dutch and the United Kingdom national guidelines, the preferred treatment regimen for resectable esophageal cancer (T1-3, N0-3, M0-1A) is neoadjuvant chemoradiation followed by radical transhiatal or transthoracic surgery. For squamous-cell carcinoma, chemoradiation alone is also a curative option[8]. The choice for the type of surgery is based on tumor stage, tumor location, lymph node involvement, and the condition of the patient. Transthoracic esophagectomy generally results in a higher lymph node yield and a trend to a higher 5-year overall survival, but also in a higher mortality and morbidity rate[4;9;10]. Surgical treatment of esophageal cancer has a high rate of post-operative complications, especially in patients with multiple co-morbidities and a higher age[9;11;12]. Hence, elderly and vulnerable patients might not be eligible for potentially curative surgical treatment[5]. Patients with an irresectable tumor, or patients who are too vulnerable for surgery are often proposed for definitive chemoradiation or palliative options only[13-16].

Due to regionalisation and centralisation in the Netherlands, surgical and EMR treatment is mainly performed in regional referral centres in which patients are discussed in a multidisciplinary team (MDT) and managed accordingly[17]. However, patients who are not referred to a regional referral centre are discussed in an MDT of the local hospital of diagnosis in which less experience in the possibilities of surgical and endoscopic treatment for esophageal cancer is available. A recent study by our group showed that hospital of diagnosis plays a significant role on the probability to receive potentially curative treatment[18]. Several factors may play a role in the decision whether patients are eligible candidates for surgery, like tumor characteristics, age and co-morbidity. The Eindhoven Cancer Registry (ECR) has a prospective registration of co-morbidity, which provides a unique possibility to examine the role of this factor in relation to others. Furthermore, most studies focus on results of patients who received potentially curative treatment in individual centres and not on the whole group of patients diagnosed with esophageal cancer, including those that have not received curative treatment. Therefore, the aim of this population-based study is to determine which factors influenced overall survival and whether these factors play a role in the decision to propose potentially curative treatment in patients with resectable esophageal cancer.

Materials and methods

Population-based data from the ECR, which is maintained by the Comprehensive Cancer Centre South, were used. The ECR collects data for all patients with newly diagnosed cancer in a large part of the southern Netherlands, which comprises about 2.3 million inhabitants. This population-based registry includes ten community hospitals, six pathology departments, and two radiotherapy institutions.

Information on age, sex, socioeconomic status (SES), co-morbidity, histology, tumor stage (classified by the International Union Against Cancer (UICC) TNM 6)[19], tumor location (according to International Classification of Diseases for Oncology (ICD-O-3))[20], and treatment is routinely extracted from the medical records by specially trained administrators of the cancer registry. Tumor location was classified as proximal (above tracheal bifurcation, C15.0, C15.1, C15.2 and C15.3), mid (between tracheal bifurcation and gastro-esophageal junction, C15.4), distal (gastro-esophageal junction, C15.5) and overlapping or not otherwise specified (C15.8, C15.9).

Clinical tumor stage was determined by at least endoscopy, CT scanning of the chest and abdomen and ultrasound of the supraclavicular nodes. Since PET CT or Endoscopic Ultrasound (EUS) were not mandatory according to the guidelines, they were only performed when indicated. Definitive tumor stage was determined as the pathologic (post-operative) stage or if not available as the clinical tumor stage.

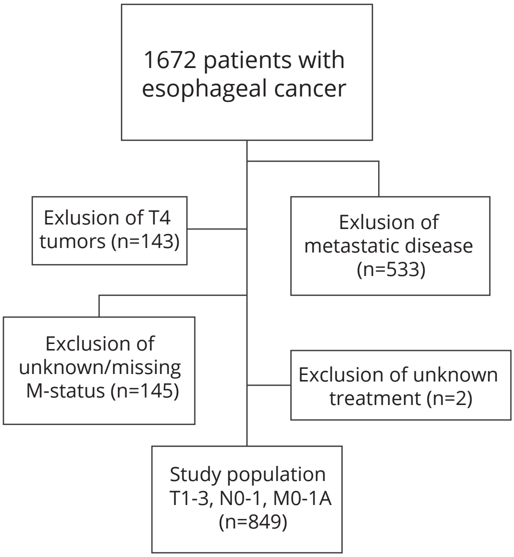
Information on medical history and co-morbidity was based on a modified list of the Charlson co-morbidity index[21]. We excluded hypertension as co-morbidity, since it is generally regarded as a minor co-morbidity. Individual SES, based on fiscal data on the value of the home and household income, is provided at an aggregated level for each postal code[22].

Surgery with a potentially curative intent was defined as an esophagectomy, multi-organ surgery or surgery not otherwise specified. Definitive chemoradiation was defined as the combination of radiotherapy and chemotherapy as the primary treatment with a curative intent. Hormone therapy, immunotherapy, local tumor surgery, palliative therapies in general, and palliative therapy of metastases were defined as "other" therapy. Treatment with no curative intent included radiotherapy alone, chemotherapy alone, and other therapy.

Study population

Between 2003 and 2010, 1672 patients with esophageal cancer (C15) were diagnosed in the ECR region. We excluded 533 patients with metastatic disease (M1 or M1B) and 143 patients with tumors extended into surrounding organs (T4), since these patients were not all eligible for curative surgery. Furthermore, patients with an unknown or missing M-status where excluded (n=145). So, we included 851 patients with potential resectable and curable esophageal cancer according to their stage (T1-3, N0-1, M0-1A). Within this group we excluded two patients with unknown therapy, resulting in a definitive study population of 849 patients (Figure 1).

Figure 1. Flowchart study population.



Statistical analyses

Univariable and multivariable Cox proportional hazard regression analyses were performed to determine the prognostic significance of age, gender, co-morbidity, SES, tumor location, tumor differentiation, tumor stage, curative intent surgery, and chemoradiation on overall survival. Survival time was defined as time from diagnosis to death or until January 1st, 2010 for the patients who were still alive. Results were reported as hazard ratios (HR) and 95% CI. Unadjusted estimates of survival rates were made using the Kaplan-Meier method, and compared using the log-rank statistic. Univariable and multivariable logistic regression analyses were conducted to evaluate the influence of age, gender, SES, co-morbidity, clinical tumor stage, tumor differentiation, and tumor location on undergoing surgery. Results were reported as odds ratios (OR) with 95% confidence intervals (95% CI). All analyses were performed using Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). All reported p-values below 0.05 were considered statistically significant.

Results

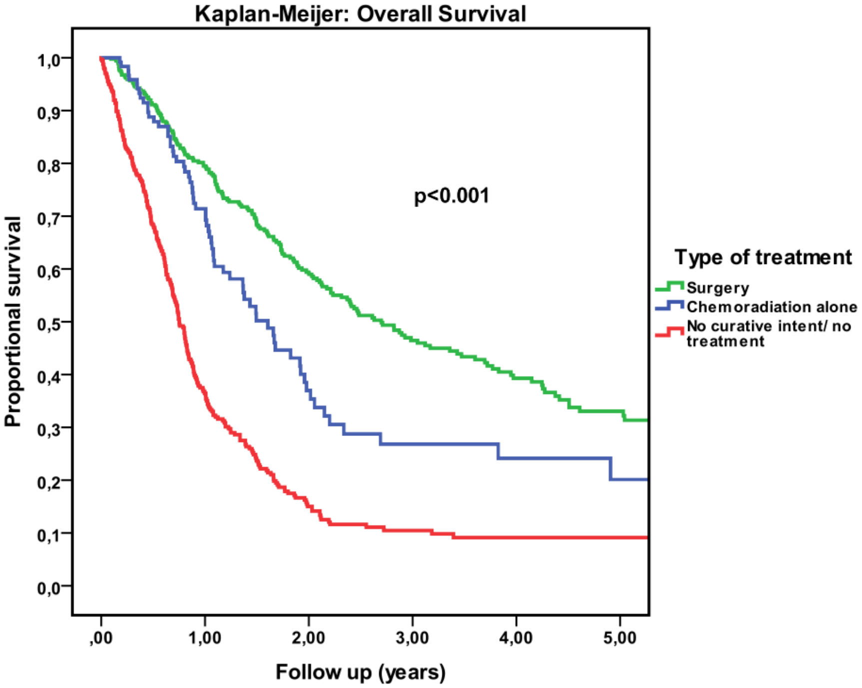
Type of treatment

From the patients with resectable esophageal cancer, 86% received any kind of treatment, thus 14% did not receive any type of treatment at all. Almost half of the patients (45%) underwent surgery (or surgery combined with other (neo)adjuvant treatment), and 15% underwent definitive chemoradiation alone. A combination treatment with (neo-adjuvant) chemoradiation and surgery was given to 17% of the patients. Throughout the years (2003 -2010) there was an increase from 12% to 34% in patients receiving this trimodality treatment. Treatment with no curative intent was administered to 26% of the patients and consisted of radiotherapy alone (20%), chemotherapy alone (2%), and other therapy (4%).

Predictors of overall survival

Patients who underwent surgery had a better 3 year overall survival compared to those who received chemoradiation alone or no curative intent/ no treatment (47% vs. 27% vs. 11%, $p<0.001$) (Figure 2). In the univariable analysis, advanced age (≥70 years), co-morbidity, being institutionalised, squamous-cell carcinomas, or high tumor stages were all associated with a worse overall survival; whereas surgery, chemoradiation alone, good tumor differentiation, and stage I were associated with better survival (Table 1). However, in the multivariable Cox regression survival analysis only surgery, chemoradiation alone, and tumor stage I were significant predictors of a better survival, whereas tumor stage III and IV were significant predictors for worse survival.

Figure 2. Overall survival of patients with esophageal cancer treated with different types of treatment.



Number at risk	0	1	2	3	4	5
Surgery	382	252	154	95	66	39
Chemoradiation alone	127	67	24	12	8	4
No curative intent/ no treatment	340	106	36	16	13	7

Table 1. Univariable and multivariable overall survival analyses for patients with esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients (n=849)	Univariable overall survival			Multivariable overall survival		
		HR[a]	95% CI	p-value	HR[a]	95% CI	p-value
Age (yrs)							
<70	484	1.0			1.0		
≥70	365	1.6	1.4-1.9	<0.001	1.0	0.9-1.3	0.686
Gender							
Male	633	1.0			1.0		
Female	216	1.1	0.9-1.3	0.406	0.9	0.7-1.1	0.467
Co-morbidity							
None	271	1.0			1.0		
1	227	1.4	1.1-1.7	0.004	1.2	0.9-1.5	0.241
2 or more	259	1.6	1.3-1.9	<0.001	1.0	0.8-1.3	0.800
Unknown	92	0.8	0.5-1.1	0.107	0.8	0.6-1.2	0.345
Type of treatment							
Surgery	382	0.3	0.3-0.4	<0.001	0.3	0.2-0.4	<0.001
Chemoradiation alone	127	0.5	0.4-0.6	<0.001	0.4	0.3-0.5	<0.001
No curative intent/ no treatment	340	1.0			1.0		
Socioeconomic status							
Low	204	1.3	1.0-1.5	0.065	1.1	0.9-1.4	0.440
Mediate	329	1.0			1.0		
High	255	0.8	0.7-1.1	0.177	0.8	0.7-1.1	0.194
Institutionalised	38	2.0	1.3-2.9	0.001	1.3	0.8-2.0	0.239
Unknown	23	0.8	0.5-1.6	0.552	0.9	0.5-1.8	0.809
Tumor location							
Proximal	52	1.2	0.9-1.7	0.222	0.8	0.5-1.1	0.171
Mid	105	1.2	1.0-1.6	0.108	1.1	0.8-1.5	0.523
Distal	655	1.0			1.0		
Overlapping/NOS[b]	37	1.4	0.9-2.1	0.103	1.1	0.7-1.7	0.725
Histology							
Squamous-cell carcinoma	271	1.3	1.1-1.5	0.011	1.2	0.9-1.5	0.159
Adenocarcinoma	537	1.0			1.0		
Other	41	1.5	1.0-2.1	0.051	1.1	0.7-1.7	0.778
Tumor differentiation							
Good	28	0.6	0.3-1.0	0.046	0.6	0.3-1.1	0.129
Moderate	219	0.8	0.7-1.0	0.072	0.8	0.6-1.0	0.069
Poor	325	1.0			1.0		
Anaplastic	8	1.5	0.7-3.1	0.333	0.8	0.3-1.8	0.525
Unknown	269	1.0	0.8-1.2	0.879	0.7	0.6-0.9	0.005
Tumor stage							
I	110	0.5	0.3-0.7	<0.001	0.4	0.2-0.6	<0.001
II	214	1.0			1.0		
III	172	1.7	1.3-2.2	<0.001	1.7	1.3-2.2	<0.001
IV	81	3.1	2.3-4.2	<0.001	2.5	1.8-3.4	<0.001
Unknown	272	2.5	2.0-3.2	<0.001	1.5	1.2-2.0	0.002

a A higher risk of dying is denoted by a hazard ratio (HR) value >1 and a lower risk of dying by a HR value <1.

b Not otherwise specified.

Predictive factors for surgery

In the univariable analysis age, gender, SES, co-morbidity, cT-stage, cN-stage, histology, and tumor location all had a significant influence on the probability to receive surgery (Table 2). In the multivariable analysis older patients (≥70 years), patients with low SES and patients with co-morbidities were less likely to receive surgery. Furthermore, patients with cT1 tumors, patients with clinically positive lymph nodes, patient with proximal tumors and patients with squamous-cell carcinomas or other carcinomas were also significantly less likely to receive surgery (Table 2).

Table 2. Predictors of surgery in patients diagnosed with resectable esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients (n=849)	Univariable analysis			Multivariable analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Age (yrs)							
<70	484	1.0			1.0		
≥70	365	0.2	0.2-0.3	<0.001	0.3	0.2-0.4	<0.001
Gender							
Male	633	1.0			1.0		
Female	216	0.6	0.4-0.8	0.001	1.1	0.7-1.6	0.728
Socioeconomic status							
Low	204	0.5	0.4-0.8	0.001	0.5	0.3-0.8	0.004
Intermediate	329	1.0			1.0		
High	255	1.1	0.8-1.6	0.453	1.1	0.7-1.6	0.620
Institutionalised	38	0.3	0.2-0.7	0.005	0.5	0.2-1.3	0.169
Unknown	23	1.4	0.6-3.2	0.466	1.5	0.6-3.8	0.413
Co-morbidity							
None	271	1.0			1.0		
1	227	0.6	0.4-0.8	0.001	0.6	0.4-1.0	0.038
2 or more	259	0.3	0.2-0.4	<0.001	0.3	0.2-0.5	<0.001
Unknown	92	0.5	0.3-0.8	0.003	0.5	0.3-0.8	0.009
Clinical T stage							
T1	47	0.6	0.3-1.0	0.062	0.5	0.2-0.9	0.026
T2	102	1.2	0.8-1.9	0.416	1.4	0.8-2.5	0.188
T3	313	1.0			1.0		
TX/missing	387	0.3	0.2-0.5	<0.001	0.4	0.2-0.5	<0.001
Clinical N Stage							
N0	375	1.0			1.0		
N1	349	0.8	0.6-1.1	0.125	0.4	0.3-0.6	<0.001
NX/missing	125	0.4	0.3-0.6	<0.001	0.6	0.4-1.0	0.063
Histology							
Squamous-cell carcinoma	271	0.5	0.4-0.7	<0.001	0.7	0.4-0.98	0.040
Adenocarcinoma	537	1.0			1.0		
Other	41	0.3	0.1-0.6	0.001	0.3	0.1-0.7	0.005
Tumor location							
Proximal	52	0.1	0.0-0.2	<0.001	0.1	0.0-0.2	<0.001
Mid	105	0.5	0.3-0.8	0.003	0.6	0.4-1.1	0.111
Distal	655	1.0			1.0		
Overlapping/ NOS[a]	37	0.5	0.3-1.1	0.078	0.7	0.3-1.6	0.390

a Not otherwise specified.

Predictive factors for chemoradiation alone.

In ther univariable analysis cT-stage, cN-stage, histology and tumor location all had a significant influence on the probability to receive chemoradiation alone. In the multivariable analysis older patients and patients with cT1 tumors were less likely to receive chemoradiation alone. Patients with clinically positive lymph nodes or a proximal tumor were more likely to receive chemoradiation alone (Table 3).

Table 3. Predictors of chemoradiation alone in patients diagnosed with resectable esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients	Univariable analysis			Multivariable analysis		
	(n=849)	OR	95% CI	p-value	OR	95% CI	p-value
Age (yrs)							
<70	484	1.0			1.0		
≥70	365	0.8	0.6-1.2	0.277	0.6	0.4-0.9	0.028
Gender							
Male	633	1.0			1.0		
Female	216	1.4	0.9-2.2	0.091	1.1	0.7-1.9	0.676
Socioeconomic status							
Low	204	1.2	0.7-1.9	0.457	1.1	0.6-1.9	0.862
Intermediate	329	1.0			1.0		
High	255	1.1	0.7-1.7	0.733	1.3	0.8-2.3	0.299
Institutionalised	38	0.3	0.1-1.4	0.139	0.5	0.1-2.4	0.376
Unknown	23	1.7	0.6-4.7	0.335	2.0	0.6-7.1	0.278
Co-morbidity							
None	271	1.0			1.0		
1	227	1.4	0.8-2.2	0.220	1.3	0.7-2.3	0.445
2 or more	259	1.0	0.6-1.6	0.865	0.8	0.4-1.4	0.421
Unknown	92	1.0	0.5-2.0	0.979	1.0	0.5-2.3	0.948
Clinical T stage							
T1	47	0.2	0.1-0.8	0.019	0.2	0.1-0.7	0.014
T2	102	0.8	0.5-1.5	0.558	0.9	0.5-1.8	0.784
T3	313	1.0			1.0		
TX/missing	387	0.3	0.2-0.5	<0.001	0.2	0.1-0.3	<0.001
Clinical N Stage							
N0	375	1.0			1.0		
N1	349	2.9	1.0-8.4	0.049	3.1	1.1-9.2	0.039
NX/missing	125	13.8	5.5-34.3	<0.001	28.7	11.0-75.0	<0.001
Histology							
Squamous-cell carcinoma	271	2.7	1.8-3.9	<0.001	1.9	1.1-3.2	0.023
Adenocarcinoma	537	1.0			1.0		
Other	41	2.5	1.1-5.4	0.025	1.4	0.5-3.5	0.504
Tumor location							
Proximal	52	4.9	2.7-8.9	<0.001	2.3	1.1-5.0	0.033
Mid	105	1.8	1.1-3.1	0.031	0.9	0.5-1.9	0.868
Distal	655	1.0			1.0		
Overlapping/ NOS[a]	37	1.1	0.4-3.0	0.815	0.9	0.3-2.8	0.893

a Not otherwise specified.

Discussion

In our population-based study of patients with potentially resectable esophageal cancer the curative resection rate was 45%, which is relatively high. Other studies found overall resection rates of 34% to 41%[5;23]. However, these studies had a slightly different study population which also included patients with T4 tumors. We found that 14% of the study population did not receive any kind of treatment, which might be caused by the patient choice for no treatment. Furthermore, we showed that surgery was an independent predictor for a better survival when compared with no curative intent treatment/ no treatment (HR 0.3; 95% CI 0.2-0.4). This is in concordance with other studies with comparable hazard ratios favouring surgery[5;23]. Recent analysis of population based SEER data confirmed that surgery is an independent predictor for a better 5- and 10-year overall survival when compared with no surgery[7].

Trimodality treatment containing neo-adjuvant chemoradiation followed by surgery has recently become standard treatment in the Netherlands[8]. In our study only 144 patients (17%) were offered this therapy regimen, which is probably due to the fact that our study has started in 2003 and randomized trials studying neoadjuvant chemoradiation like the CROSS trial were still ongoing[24]. Guidelines in that period did not advice neoadjuvant chemoradiation as standard treatment, however we observed an increase in use of this trimodality treatment from 12% to 34%. Definitive chemoradiation might also be an option for patients with advanced age and/or multiple co-morbidities or locally advanced tumors[14-16;25;26]. Chemoradiation alone was a significant predictor for a better survival in our multivariable survival analysis with a hazard ratio of 0.4 (95% CI 0.3-0.5) when compared with no curative intent/no treatment at all. A recent study showed no survival difference between chemoradiation alone and chemoradiation combined with surgery (hazard ratio of 1.01 (95%CI 0.90–1.13)[23]. These results suggest the need for further research on the role of definitive chemoradiation vs. neoadjuvant chemoradiation followed by surgery in patients with esophageal cancer.

We observed that patients aged ≥70 yrs were significantly less likely to undergo surgery, which is in line with other observations[5]. A recent Dutch study showed that age ≥70 yrs was a risk factor for surgical complications and post-operative mortality[27]. Others have shown similar results with a significantly increased risk for in-hospital mortality for patients aged ≥ 70 yrs[11]. In our multivariable analysis older patients (≥70 yrs) were less likely to receive chemoradiation alone. In a study conducted in the United States in which they analysed toxicity after chemoradiation in the elderly (>75yrs), only fifty percent of the patients completed the planned chemoradiation and 71% of the patients experienced adverse events during treatment that required hospitalization, emergency department visit, and/or treatment break[28].

We did not observe an independent effect of advanced age on overall survival. This in contrast to other studies, in which age was a significant predictor for worse overall and disease-specific survival in a large study from the Netherlands and the United Kingdom[11;27].This difference might be explained by the inclusion of all patients diagnosed with resectable (T1-3, N0-1, M0-1A) esophageal cancer in our study. This is in contrast with the other studies in which they included only patients who underwent surgery and thus a potential selection bias could play a role[11;27]. Furthermore, co-morbidity appears to play an important role in decision making, since multiple co-morbidities are a significant predictor to be detained from potentially curative surgery in our study, which is in concordance with others in which the Romano-Charlson score of 1 or more was an independent predictor for not receiving surgery[5]. An Australian study showed that the number of co-morbidities predicted post-operative morbidity like pneumonia, respiratory failure, and overall pulmonary morbidity[29]. Respiratory co-morbidity has been shown to be an independent predictor for non-surgical complications and post-operative mortality but not for disease-specific 5-year survival[27]. Co-morbidity has also been shown to be an independent predictor for survival in colon, rectal, breast, and prostate cancer[21].

We showed that low SES was a significant predictor for not receiving surgery compared with intermediate SES. Others have also associated low SES with a smaller chance to be referred for surgery[5]. Another Dutch population-based study also showed that resections are more often performed in patients with a higher SES[30]. Since many other factors may be associated with SES, it would be tentative to conclude that SES is an important independent determinant in decision-making. Furthermore, a study from the south-east London Cancer Network showed no difference between the highest and lowest income quintiles for the chance to be proposed for surgery[31]. In addition, once operated upon, SES did not influence overall survival in this study, which is comparable with others[32].

Histological type of tumor was in our study an independent predictor for surgery and chemoradiation alone. Patients with squamous-cell and other carcinomas were less often associated with referral for surgery compared to patients with an adenocarcinoma, which is in concordance with others[33]. This might be due to the fact that most distal tumors are adenocarcinomas and proximal tumors are more often squamous-cell carcinomas. In our study proximal tumors are indeed less likely to be treated surgically, but more likely to be treated with chemoradiation alone. Considering these results, it is remarkable that histological type of tumor and tumor location were no independent predictors for survival in our study. On the other hand, these results are in concordance with a study in which no significant difference on disease specific survival between adenocarcinoma and squamous-cell carcinoma was observed[27]. However, distal tumors were shown to have a tendency to a better overall survival[23]. As expected, clinical T and N stage were independent predictors for receiving surgery or definitive chemoradiation in our study. Furthermore, patients with a cT1 tumor were less likely to receive surgery or definitive chemoradiation in our study, which is probably caused by the upcoming use of Endoscopic Mucosal Resection (EMR). Tumor and lymph node stage, when known preoperatively, are thus relevant factors for decision making whether or not a patient could be proposed for surgery or definitive chemoradiation. Furthermore, this seems reasonable since tumor stage is an independent predictor for disease-specific survival, disease-free survival, and overall survival[34].

This study included patients with potentially resectable and curable esophageal cancer. We excluded patients with distant metastasis (M1B-M1) as well as patients with unknown or missing M-status. Excluding patients with unknown or missing M-status might give some selection bias, however we aimed to assure that we included only patients with a potentially resectable and curable tumor. All T4 tumors were excluded, since in the ECR it was not possible to determine T4 tumors which might be eventually resectable with or without neo-adjuvant treatment. In the ECR, clinical T-stage was determined by the results from endoscopy, CT scan, and EUS. Since EUS was not performed in all patients there are many missing clinical T stage values (n=387). However, for determining resectability of an esophageal tumor EUS has been shown not to be necessarily needed[35].

The question remains whether other factors might play a role in the decision to propose patients for curative treatment, since that decision is a multifactorial process in which patient characteristics and doctors preferences may both play a role. Unfortunately data on factors like nutritional status and tolerance of neoadjuvant treatment which might play a role in decision making are not available for this analysis. Furthermore, all patients are discussed within local multidisciplinary team meetings however, not in all MDT's participate regional experts knowing all possibilities of esophageal cancer treatment. Multidisciplinary meetings within expert centres have shown to be important for decision making in esophageal cancer. In a recent study, in 35% of patients with esophageal cancer, the initially proposed plan was altered after the multidisciplinary meeting[36].

In conclusion, treatment modalities including surgery and chemoradiation alone as well as stage of disease were independent predictors of a better overall survival in patients with potentially resectable esophageal cancer. Therefore, the decision to perform potentially curative treatment is of crucial importance to improve overall survival for patients with potentially resectable esophageal cancer. Although age and socioeconomic status had no significant influence on overall survival, a higher age and low socioeconomic status negatively influenced the probability to propose potentially curative treatment.

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CHAPTER 3

Definitive chemoradiation or surgery in elderly patients with potentially curable esophageal cancer in the Netherlands: a nationwide population-based study on patterns of care and survival

Authors:

M. Koëter, MD[1]; M. van Putten, Msc[2]; R.H.A. Verhoeven, PhD[2]; V.E.P.P. Lemmens, PhD[2,3]; G.A.P. Nieuwenhuijzen, MD, PhD[1].

Affiliations:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands.

[2] Department of Research,
Netherlands Comprehensive Cancer Organisation (IKNL), The Netherlands.

[3] Department of Public Health,
Erasmus University Medical Centre Rotterdam, The Netherlands.

Abstract

Introduction: The aim of our study was to describe treatment patterns and the impact on overall survival among elderly patients (75 years and older) with potentially curable esophageal cancer.

Methods: Between 2003 and 2013, 13244 patients from the nationwide population-based Netherlands Cancer registry were diagnosed with potentially curable esophageal cancer (cT2-3,X, any cN, cM0,X) of which 34% were elderly patients (n=4501).

Results: Surgical treatment with or without neoadjuvant treatment remained stable among elderly patients (around the 16% between 2003-2013). However, among younger patients surgical treatment increased from 60.2% to 67.0%. The use of definitive chemoradiation (dCRT) increased in elderly patients from 1.9% to 19.5% and in younger patients from 5.2% to 17.2%. Due to the increase in dCRT, treatment with curative intent doubled in the elderly from 17% to 37.1%. Multivariable Cox regression revealed that elderly patients with an adenocarcinoma receiving surgery alone or dCRT had a significantly worse overall survival compared to those receiving surgery with neoadjuvant chemo(radio)therapy (nCRT/CT) (HR: 1.7 95%CI 1.4-2.0 and HR=1.9 95%CI 1.5-2.3). However, among elderly with squamous cell carcinoma overall survival was comparable between dCRT, surgery alone and surgery with nCRT/CT.

Conclusion: Survival was comparable among elderly patients with squamous cell carcinoma who underwent surgery with nCRT/CT, surgery alone or received dCRT, while elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a better overall survival, when compared with surgery alone or dCRT. Therefore, dCRT can be considered as a reasonable alternative for surgery among potentially curable elderly patients with esophageal squamous cell carcinoma. However in elderly patients with esophageal adenocarcinoma surgery with nCRT/CT is still preferable regarding overall survival.

Introduction

The incidence of esophageal cancer, especially adenocarcinoma, has increased dramatically over the past four decades in the Western world and is still rising but at a slower rate than previously[1,2]. Esophageal cancer is mainly a disease of the elderly as a significant number of patients is aged between 60 and 85 year at time of diagnosis[3,4]. In the Netherlands approximately 30% of all newly diagnosed patients with esophageal cancer is 75 years or older[5].

According to the Dutch clinical practice guidelines, the preferred treatment for patients with potentially curable esophageal cancer is neoadjuvant chemoradiation followed by a subsequent esophagectomy. Early esophageal cancer (T1a) can be treated with Endoscopic Mucosal Resection (EMR)[6]. Frail patients unfit for surgery, such as some elderly patients, can be treated alternatively with a curative intention using definitive chemoradiation (dCRT)[7,8]. Furthermore, histological subtype plays a role in treatment of patients with potentially curable esophageal cancer. For example, patients with squamous cell carcinoma seem to have a better response to dCRT compared to patients with an adenocarcinoma[9,9-11]. Surgical treatment of esophageal cancer is complex with a high post-operative complication rate, especially in elderly patients with multiple co-morbidities, which might be an argument to withhold some patients from surgical treatment[12,13]. A previous study has shown an increase in 30-day postoperative mortality from 4.9% in patients younger than 65 years to 10.3% in patients older than 75 years[14].

However, most treatment strategies and guidelines are based on clinical trials in which elderly patients are excluded. Therefore, it is of significant importance to investigate the effect of different treatment options on survival in this specific group of patients. The aim of our study was to describe treatment patterns and the impact on overall survival in elderly patients (75 years and older) with potentially curable esophageal cancer (adenocarcinoma or squamous cell carcinoma) in the Netherlands.

Patients and Methods

Data collection

Nationwide population-based data from the Netherlands Cancer Registry (NCR) were used. The NCR is 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, radiotherapy institutions and diagnosis therapy combinations (specific codes for reimbursement purposes). Specially trained data managers of the NCR routinely extracted information on diagnosis, tumor stage and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands were registered. Institutional Review Board approval was obtained from the NCR.

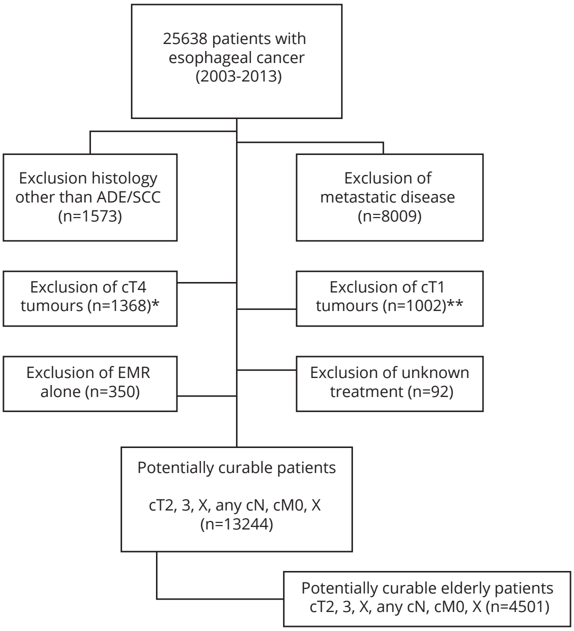
Patients

Between January 2003 and December 2013, 25.638 patients were diagnosed with an adenocarcinoma or squamous cell carcinoma of the esophagus or gastro-esophageal junction in the Netherlands. The topography and morphology of the tumors were coded according to the International Classification of Diseases for Oncology (ICD-O-3)[15]. Subsite distribution was divided as: proximal (C15.0, C15.3), mid (C15.4), distal (C15.5), overlapping or not otherwise specified (C15.8, C15.9) and gastro-esophageal junction (GEJ) (C16.0). Patients diagnosed from 2003 to 2009 were staged according to TNM-6, whereas patients diagnosed from 2010-2013 were staged according to TNM-7 [16,17].

Patients with potentially curable esophageal tumors were eligible for this study (Figure 1). Patients were considered potentially curable in this study if they had no clinically distant metastasis (cM1b for TNM-6 and cM1 for TNM 7) (n=8009) and no tumors infiltrating surrounding organs (cT4 according to TNM-6 and cT4A and cT4B according to TNM-7) (n=1368). We excluded patients with tumors infiltrating surrounding organs since it was uncertain whether or not these patients were eligible for curative treatment. For the analyses, patients with a cM1A tumor according to TNM-6 were categorized as having cN+ as most patients with a cM1A tumor had a distal tumor with coeliac lymph nodes which can be considered as having cN+ according to TNM-7. Furthermore, patients with unknown clinical distant metastases (cMX) were included. It should be noted that as of 2010 coding regulations to register a cM0 or cM1 status into the NCR were less strict than before 2010, and therefore as of 2010 relatively more patients were registered with a cM0 rather than a cMX into the NCR. To account for this, we decided to include all patients with cMX. Patients with an in-situ or a cT1 tumor (n=1002) were also excluded since these tumors are treated predominantly with an Endoscopic Mucosal Resection (EMR) rather than surgical treatment. In addition, patients with missing/unknown treatment (n=92) and patients receiving

EMR alone (n=350) were excluded. This resulted in 13.244 patients with a potentially curable esophageal carcinoma (cT2, 3, X, any cN, cM0, X). Of these patients 4501 (34%) were elderly patients being 75 years and older (Figure 1).

Figure 1. Flowchart of the study population.



*cT4 according to TNM-6 and cT4a and cT4b according to TNM-7.

**cT1 according to TNM-6 and cT1a and cT1b according to TNM-7.

Treatment

Surgery with potentially curative intent was defined as an transhiatal esophagectomy or transthoracic esophagectomy. Definitive chemoradiation (dCRT) was defined as the combination of radiotherapy and chemotherapy as primary treatment without surgery. Curative treatment was defined as dCRT, surgery alone or surgery with neoadjuvant chemoradiotherapy or chemotherapy (nCRT/CT). All other treatments were defined as “other” therapy.

Statistical analysis

Differences in patient and tumor characteristics between elderly patients with an adenocarcinoma and squamous cell carcinoma were described and compared using the Pearson’s Chi-square test for nominal data. For differences in continuous variables, the independent T-test was used. Survival time was defined as time from diagnosis to death or until February 1st 2016 for patients who were still alive. Survival curves per treatment option were obtained using the Kaplan-Meier method for elderly patients according to histology. Differences in overall survival according to treatment were assessed by using log-rank tests. Multivariable Cox regression analyses were performed to evaluate independent prognostic factors for overall survival. All statistical analyses were performed using Statistical Package for Social Sciences version 22.0 (IBM Corporation, Armonk, NY, USA) and P-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

Of the potentially curable elderly patients of 75 years and older diagnosed with an esophageal carcinoma, 75.6% (n=3402) was diagnosed with an adenocarcinoma and 24.4% (n=1099) with a squamous cell carcinoma. There were no significant differences in age, cT- stage, cN-stage and cM-stage between both histology groups. However, patients with an adenocarcinoma had more often a distally located tumor and a poor tumor differentiation. Furthermore, elderly patients with an adenocarcinoma more often received surgical treatment (21.3%) than dCRT (7.7%), whereas patients with a squamous cell carcinoma more often received dCRT (13.1%) than surgery (10.4%) (Table 1). Of all elderly patients diagnosed with potentially curable esophageal carcinoma, 6.9% received surgery with nCRT/CT, 11.8% received surgery alone, 18.6% received surgery, 9.0% received dCRT and 72.4% received other/no treatment.

Table 1. Patient characteristics of the elderly patient (≥75 years) diagnosed with potentially curable esophageal cancer in the period 2003-2013 (n=4501).

	Adenocarcinoma	**Squamous cell carcinoma**	
Total N= 4501	3402 (75.6%)	1099 (24.4%)	P-value
Mean age	81.6 (SD 4.9)	81.3 (SD 5.0)	0.051
Gender:			
Male	2374 (69.8%)	514 (46.8%)	
Female	1028 (30.2%)	585 (53.2%)	<0.001
cT-stage:			
2	582 (17.1%)	171 (15.6%)	
3	863 (25.4%)	308 (28.0%)	
Unknown/missing	1957 (57.5%)	620 (56.4%)	0.163
cN-stage			
N0	1167 (34.3%)	388 (35.3%)	
N+	1173 (34.5%)	395 (35.9%)	
Unknown/missing	1062 (31.2%)	316 (28.8%)	0.302
cM-stage			
M0	2790 (82.0%)	921 (83.8%)	
Unknown/missing	612 (18.0%)	178 (16.2%)	0.174
Tumor location:			
Proximal	38 (1.1%)	164 (14.9%)	
Mid	208 (6.1%)	398 (36.2%)	
Distal	1983 (58.3%)	454 (41.3%)	
GEJ[a]	1040 (30.6%)	7 (0.6%)	
Overlapping/NOS[b]	133 (3.9%)	76 (6.9%)	<0.001
Differentiation:			
Well	67 (2.0%)	31 (2.8%)	
Moderate	677 (19.9%)	296 (26.9%)	
Poor	1147 (33.7%)	254 (23.1%)	
Unknown	1511 (44.4%)	518 (47.1%)	<0.001
Type of treatment			
Surgery with nCRT/CT[c]	250 (7.3%)	59 (5.4%)	
Surgery alone	475 (14.0%)	55 (5.0%)	
Definitive chemoradiation	261 (7.7%)	144 (13.1%)	
Other/no treatment	2416 (71.0%)	841 (76.5%)	<0.001

[a] Gastro-esophageal junction

[b] Not otherwise specified

[c] Among this group of patients 77.3% received nCRT and 22.7% received CT. Two patients received CRT postoperatively.

Trends in treatment

From 2003 until 2013, the use of surgery with nCRT/CT among the elderly (≥75 years) and the younger patients (<75 years) increased over time from 0.5% to 13.5% and from 14.4% to 63.3% respectively. In line with these findings, the proportion of patients with underwent surgery alone decreased among both the elderly and the younger patients from respectively 14.5% to 4.2% and from 45.8% to 3.7%. The use of surgical treatment (surgery with nCRT/CT or surgery alone) among all elderly patients (≥75 years) remained relatively stable over time from 15.0% in 2003 to 17.7% in 2013, whereas among the younger patients (≥75 years) the use of surgical treatment increased over time from 60.2% in 2003 to 67.0% in 2013. Furthermore, there was an increase in administration of dCRT in elderly patients from 1.9% to 19.5% as well as in the younger patients from 5.2% to 17.2% (Figure 2a). The increase in dCRT was most prominent among elderly patients with a squamous cell carcinoma in which treatment with dCRT increased from 3.5% to 30.7%, while among younger patients with squamous cell carcinoma an increase from 9.5% to 29.3% was observed (Figure 2b). In patients with an adenocarcinoma, the increase in use of dCRT was comparable in the elderly patients compared to the increase among younger patients (Figure 2c). Mainly due to the increase in dCRT, the administration of treatment with curative intent (surgery or dCRT) doubled over time in all elderly patient from 17% to 37.1%. The increase of treatment with a curative intent quadrupled over time in the elderly patient with squamous cell carcinoma from 10.5% to 41.2%. However, the increase in the use of treatment with curative intent was less prominent in the younger patients (Figure 2).

Figure 2. Trends in treatment of patients with esophageal carcinoma according to age and histology.
Figure 2a. Trends in treatment of all patients with esophageal carcinoma.

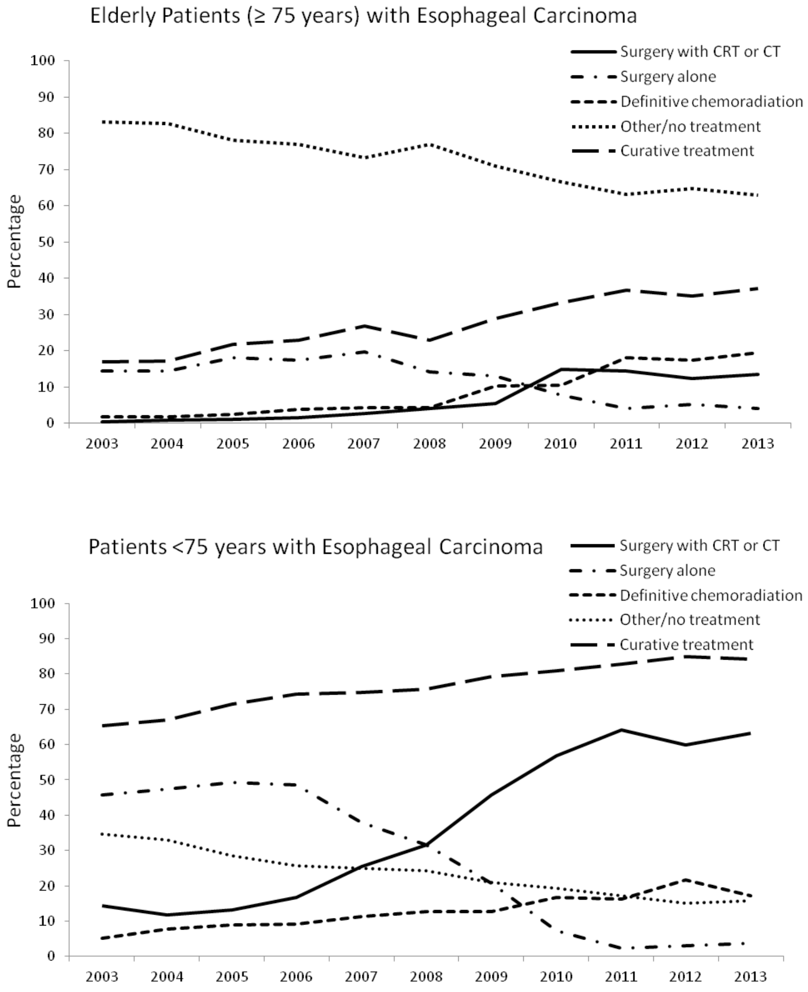


Figure 2b. Trends in treatment of patients with a squamous cell carcinoma.

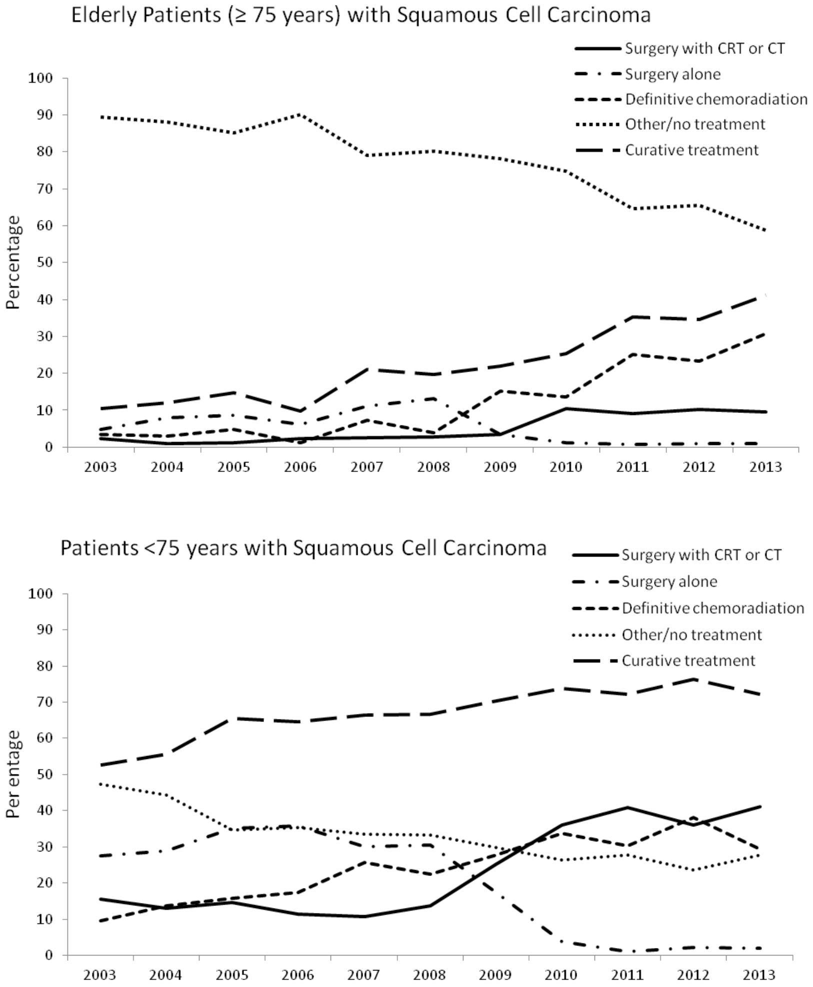
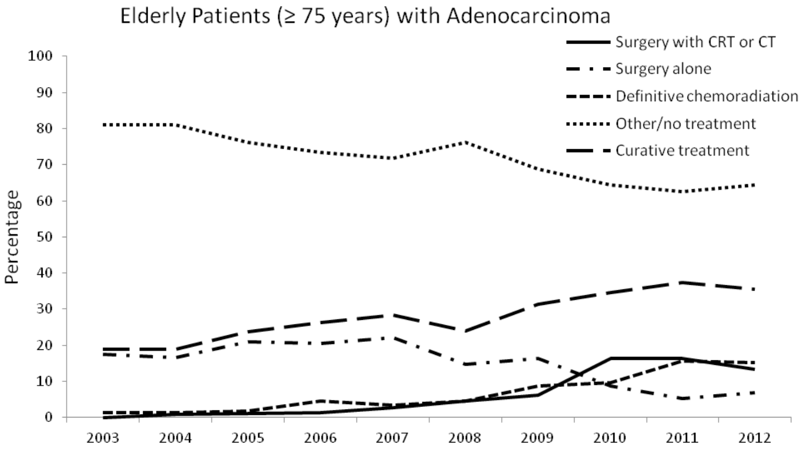
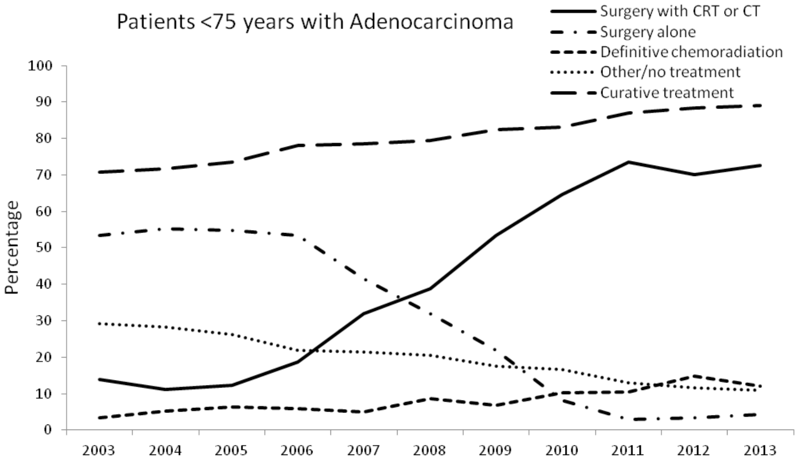


Figure 2c. Trends in treatment of patients with an adenocarcinoma.





Survival

Overall, elderly patients with a potentially curable adenocarcinoma had a comparable 1- and 3-year overall survival rate compared to elderly patients with a potentially curable squamous cell carcinoma with 1-year overall survival rates of 40.8% vs. 36.5% and 3-year survival rates of 12.0% vs. 14.1%, respectively (log rank p=0.621). Furthermore, the 1- year overall survival in elderly patients with an adenocarcinoma treated with surgery and nCRT/CT was 79.6% which was comparable to the overall survival of patients treated with surgery alone (64.8%) or dCRT (72.4%) whereas 3-year overall survival was significantly better for patients who underwent surgery with nCRT/CT (51.2%) compared to patients receiving surgery alone (29.5%) or dCRT (11.6%) (p<0.001) (Figure 3a). Among elderly patients with a squamous cell carcinoma, patients receiving surgery with nCRT/CT had a better 3-year overall survival (50.2%) compared to surgery alone (40.0%) and dCRT (36.8%) however this difference was not statistically significant (p=0.267) (Figure 3b). Multivariable Cox regression analyses showed that patients with male gender, a poor tumor differentiation, an overlapping tumor/not otherwise specified tumor location, cT3 tumors, regional lymph nodes metastasis and a squamous cell histology had a significantly worse overall survival. Regarding the treatment strategy, the multivariable Cox regression analysis which included both histologies showed that elderly patients who received surgery alone (Hazard ratio [HR]: 1.6, 95% confidence interval [CI] 1.3-1.9), dCRT (HR: 1.7, 95% CI 1.4-2.0) or other/no treatment (HR:4.1, 95% CI 3.5-4.8) had a significantly worse overall survival compared to patients who underwent surgery with nCRT/CT (Table 2). Comparable results were found for elderly patients with an adenocarcinoma. Among elderly patients with an adenocarcinoma, patients receiving surgery alone (HR: 1.7, 95% CI 1.4-2.0), dCRT (HR: 1.9, 95% CI 1.5-2.3) or other/no treatment (HR: 4.3, 95% CI 3.6-5.1) had a significantly worse overall survival compared to patients receiving surgery with nCRT/CT. However, among elderly patients with a squamous cell carcinoma overall survival was comparable for patients who underwent surgery alone (HR: 1.3, 95% CI 0.8-2.1), dCRT (HR: 1.4, 95% CI 0.9-2.0) or surgery with nCRT/CT (Table 2).

Figure 3a. Kaplan-Meier survival analysis among elderly patients with an adenocarcinoma (n=3402).

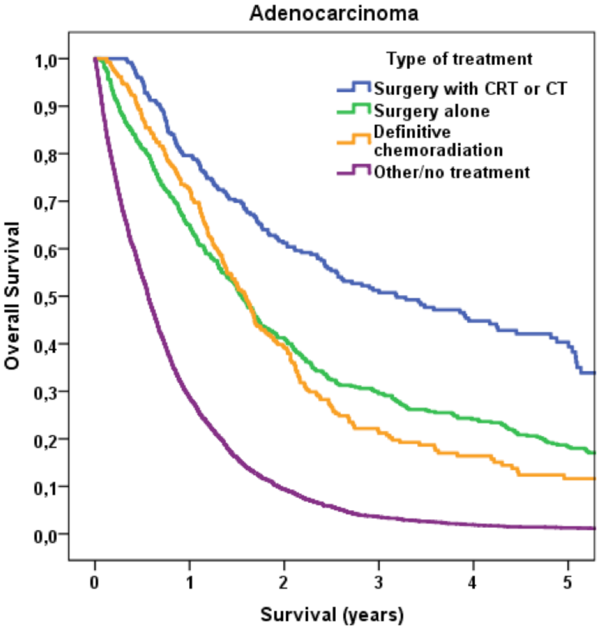


Figure 3b. Kaplan-Meier survival analysis among elderly patients with a squamous cell carcinoma (n=1099).

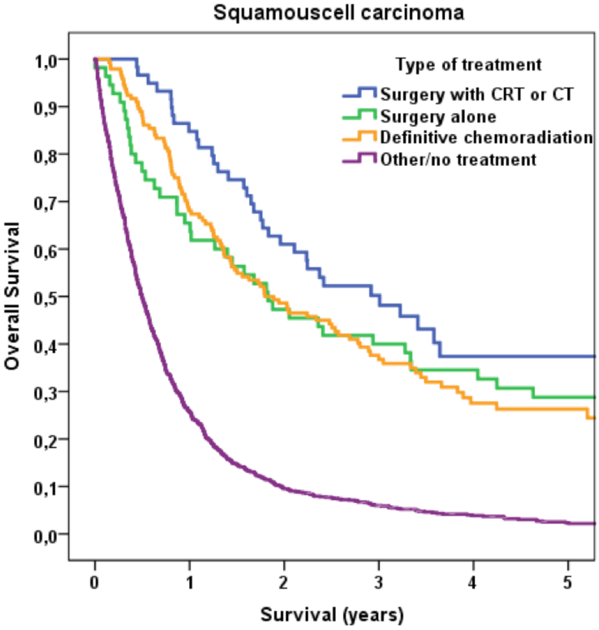


Table 2. Multivariable Cox survival analysis for all elderly patients and according to histology

Multivariable analysis*	**All elderly patients (N=4501)**			**Adenocarcinoma (N=3402)**			**Squamous cell carcinoma (N=1099)**		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Gender									
Male	1.0			1.0			1.0		
Female	0.9	0.8-1.0	0.001	0.9	0.8-1.0	0.015	0.8	0.7-0.9	0.003
Period of diagnosis									
2003-2006	0.9	0.9-1.0	0.084	0.9	0.8-1.0	0.058	1.0	0.8-1.1	0.581
2007-2010	0.9	0.9-1.0	0.085	1.0	0.9-1.0	0.304	0.9	0.7-1.0	0.097
2011-2013	1.0			1.0			1.0		
Tumor differentiation									
Well	0.8	0.6-1.0	0.031	0.6	0.5-0.8	0.001	1.7	1.1-2.5	0.009
Moderate	0.9	0.8-0.9	<0.001	0.8	0.7-0.9	<0.001	1.1	0.9-1.3	0.269
Poor	1.0			1.0			1.0		
Unknown/missing	0.8	0.8-0.9	<0.001	0.8	0.7-0.8	<0.001	1.0	0.8-1.2	0.922
Tumor location									
Proximal	0.8	0.7-0.9	0.008	1.0	0.7-1.4	0.954	0.7	0.6-0.9	0.002
Mid	0.9	0.8-1.0	0.041	1.0	0.8-1.1	0.721	0.9	0.7-1.0	0.030
Distal	1.0			1.0			1.0		
GEJ[a]	1.0	0.9-1.1	0.828	1.0	0.9-1.1	0.997	1.9	0.9-4.0	0.104
Overlapping/ NOS[b]	1.3	1.1-1.5	0.001	1.2	1.0-1.4	0.042	1.4	1.1-1.8	0.008
Clinical T-stage									
cT2	0.9	0.8-1.0	0.019	0.9	0.8-1.0	0.019	0.9	0.7-1.1	0.411
cT3	1.0			1.0			1.0		
cTunknown	1.2	1.1-1.3	<0.001	1.2	1.1-1.3	0.002	1.4	1.2-1.7	<0.001
Clinical N-stage									
cN0	1.0			1.0			1.0		
cN+	1.2	1.1-1.3	<0.001	1.2	1.1-1.3	<0.001	1.2	1.0-1.4	0.057
cNunknown	1.6	1.4-1.7	<0.001	1.5	1.4-1.7	<0.001	1.8	1.5-2.1	<0.001
Type of treatment									
Surgery with nCRT/CT	1.0			1.0			1.0		
Surgery alone	1.6	1.3-1.9	<0.001	1.7	1.4-2.0	<0.001	1.3	0.8-2.1	0.222
Def. Chemoradiation	1.7	1.4-2.0	<0.001	1.9	1.5-2.3	<0.001	1.4	0.9-2.0	0.123
Other/no treatment	4.1	3.5-4.8	<0.001	4.3	3.6-5.1	<0.001	3.8	2.7-5.4	<0.001
Histology									
Squamous cell	1.1	1.0-1.2	0.037						
Adenocarcinoma	1.0								

[a] Gastro-esophageal junction

[b] Not otherwise specified

* Adjusted for all variables listed in table 2.

Discussion

This large nationwide population-based study among elderly patients with potentially curable esophageal cancer who were 75 years or older revealed an increase in treatment with a curative intent, with a consistent use of surgical treatment and a significant increase in the use of dCRT among all elderly patients in the period 2003-2013. The increase in administration of dCRT was most prominent in elderly patients with a squamous cell carcinoma. Furthermore, multivariable analysis showed no difference in overall survival for elderly patients with a squamous cell carcinoma who received surgery with nCRT/CT or surgery alone or dCRT. However, elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a significantly better overall survival compared to patients who underwent surgery alone or dCRT.

Despite the increase in the use of treatment with curative intent among potentially curable elderly patients, explained by the increase in dCRT, there is still a large proportion of patients that were not treated with curative intent (72.4%).This study demonstrates that the elderly patients with potentially curable tumors received less often surgical treatment compared to younger patients (17.7% vs. 67.0%), whereas the use of dCRT was slightly higher in the elderly patients compared to the younger patients (19.5% vs. 17.2%). These findings may be explained by the fact that an older age is a risk factor for post-operative morbidity and mortality after esophagectomy[12,18-20]. Although, other studies have shown that age alone should not be regarded as a predictor for worse overall survival after esophagectomy, in daily practice it appears that advanced age is a significant factor in decision making whether or not patients are proposed for surgery[12,13].

Our study revealed a relatively stable use of surgical treatment and a significant increase in use of dCRT among all elderly patients during the study period especially after 2010. This striking increase in administration of dCRT is higher compared to another study in the Netherlands in an earlier period (1989-2008) in which they reported an increase from 0.19% to 2.20%[21]. The increase in use of dCRT is probably caused by the increasing awareness that dCRT has a favorable survival, especially among patients with squamous cell carcinoma, and is often well tolerated, even in patients with considerable co-morbidity[7,8]. Although toxicity after chemoradiation is occuring frequently, with 75% of the patients experiencing toxicity of grade 3 or greater, especially in the elderly patients, it is often manageable[22,23].

This study showed that elderly patients with an adenocarcinoma received more often surgical treatment compared to patients with a squamous cell carcinoma which received more often dCRT especially after 2010. These result are in line with result from a large population based study in the United States[9]. The observed difference in treatment could be explained by the fact that most studies show a better response to dCRT of squamous cell carcinomas when compared to adenocarcinoma, with a better overall survival and disease free survival in good responders[10]. On the other hand, a study from the United Kingdom on dCRT revealed a comparable overall survival and disease free survival between both histological subtypes. However patients with squamous cell carcinoma had significantly more advanced stages of disease[24]. Furthermore, a significant difference in relapse pattern has been described, with adenocarcinomas being more likely to relapse in distant sites and squamous cell carcinoma more likely to recur locally[8,24].

The multivariable Cox survival analysis revealed that elderly patients with an adenocarcinoma who received surgery with nCRT/CT have a better overall survival compared to the patients receiving surgery alone or dCRT. However, among elderly patient with squamous cell carcinomas there was no significant difference in overall survival between patients who underwent surgery with nCRT/CT, surgery alone or patients who received dCRT. Currently, there are only three randomised control trials which have directly compared dCRT with surgical treatment in patients with squamous cell carcinoma. These trials have shown comparable survival rates in patients treated with definitive chemoradiation or chemoradiation followed by surgery[11,25,26]. However, in two of the three trials elderly patients were excluded and in the third trial results were not reported for elderly patients as a separate group. Furthermore, a recent Cochrane review states that there is only low quality evidence in the literature which showed that chemoradiation appears to be equivalent to surgery in squamous cell carcinoma who are responsive to chemoradiation, however in adenocarcinoma there is uncertainty whether or not patients receiving definitive chemoradiation benefit compared to surgery[27]. Our results provide more arguments for the equivalence of definitive chemoradiation to surgery in squamous cell carcinoma and confirm their statement on adenocarcinoma. The results of our study advocate for further research in which the use of dCRT and surgery are compared for disease free survival and quality of life. Univariable and multivariable survival analysis also revealed a similar overall survival for patients with esophageal squamous cell carcinoma who underwent surgery with or without nCRT/CT. Although there seems to be immortal time bias, the Kaplan-Meier curves for these treatment groups were parallel, assuming overall survival is comparable (Figure 3b). Immortal time bias exists of patients receiving nCRT/CT which takes more time to receive than surgery alone. However, no landmark analysis was performed as this would result in exclusion of many patients in the 'other/no treatment' group. Multivariable analysis confirmed the non-significant difference in overall survival between squamous cell carcinoma patients with and without nCRT/CT. These results are in contrast with results from the CROSS trial[28,29], which showed an improved survival for patients who received surgery with nCRT compared to patients who received surgery alone. Moreover, the difference in overall survival was higher for squamous cell carcinoma compared to adenocarcinoma. However, most elderly patients did not meet the eligibility criteria from the CROSS trial. Therefore, further research should investigate the difference in outcomes between surgery with or without nCRT/CT among elderly patients with esophageal squamous cell carcinoma.

A limitation of this study is that the NCR did not register nationwide information on co-morbidity or performance status during the study period. This might have influenced the survival analyses since co-morbidity and performance status plays an important role in the clinical decision making, especially among the elderly patients and has a significant influence on overall survival. However, the survival benefit for dCRT might even be more than observed, because especially unfit patients with multiple co-morbidities and an a priori unfavorable prognosis receive dCRT. Thus, the lack of co-morbidity data might even lead to an underestimation of the potential favorable impact of dCRT on overall survival. This study has also several strengths, such as its observational nature resulting in a representative nationwide population and therefore enabling the demonstration of current patterns of care and its impact on overall survival among elderly patients with esophageal cancer in daily clinical practice.

In conclusion, this large nationwide population-based study revealed that there was a consistent use of surgical treatment and a major increase in use of dCRT among all elderly patients with potentially curable esophageal cancer in the period 2003 to 2013. The increase in dCRT was most prominent among patients with squamous cell carcinoma. Survival was comparable among elderly patients with squamous cell carcinoma who underwent surgery with nCRT/CT, surgery alone or received dCRT, while elderly patients with an adenocarcinoma who underwent surgery with nCRT/CT had a better overall survival, when compared with surgery alone or dCRT. Therefore, dCRT can be considered as a reasonable alternative for surgery among potentially curable elderly patients with esophageal squamous cell carcinoma. However in elderly patients with esophageal adenocarcinoma surgery with nCRT/CT is still preferable regarding overall survival.

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CHAPTER 4

Hospital of diagnosis and probability to receive a curative treatment for esophageal cancer

Authors:

M. Koëter MD[1]; L.N. van Steenbergen PhD[2]; V.E.P.P. Lemmens PhD[2,3]; H.J.T. Rutten MD, PhD[1,4]; J.A. Roukema MD, PhD[5]; B. P. L. Wijnhoven[6]; G.A.P. Nieuwenhuijzen MD, PhD[1]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands.

[2] Eindhoven Cancer Registry,
Comprehensive Cancer Centre South, Eindhoven, The Netherlands.

[3] Department of Public Health,
Erasmus MC, University Medical Center Rotterdam, The Netherlands.

[4] Department of Surgery,
Maastricht University Medical Centre, The Netherlands.

[5] Department of Surgery, St. Elisabeth Hospital Tilburg, The Netherlands.

[6] Department of Surgery, Erasmus MC, University Medical Center Rotterdam,
The Netherlands.

Abstract

Background: Surgical treatment of esophageal cancer in the Netherland is performed in high volume centres. However, the decision to refer patients for curative surgery is made in the referring hospital of diagnosis. The objective of this study was to determine the influence of hospital of diagnosis on the probability of receiving a curative treatment and survival.

Material and method: All patients with resectable esophageal cancer (cT1-3, cN0-1, cM0-1A) diagnosed between 2003-2010 (n=849) were selected from the population based Eindhoven Cancer Registry, an area with ten non-academic hospitals. Multivariable logistic regression analysis was conducted to examine the independent influence of hospital of diagnosis on the probability to receive curative treatment. Furthermore, the effect of hospital of diagnosis on overall survival was examined using multivariable Cox regression analysis.

Results: 849 patients were included in the study. A difference in the proportion of patients referred for surgery was observed ranging from 33% to 67% (p=0.002) between the hospitals of diagnosis. Multivariable logistic regression analysis confirmed the effect of hospital of diagnosis on the chance to undergo curative treatment (OR 0.1, 95% CI 0.1-0.4). Multivariable Cox regression analysis showed that hospital of diagnosis also had an effect on overall survival up to a hazard ratio of 2.2 (95% CI 1.3-3.7).

Conclusion: There is a strong relation between hospital of diagnosis and the chance of referring patients with esophageal cancer for a curative treatment as well as overall survival. Patients diagnosed with esophageal cancer should be discussed within a regional multidisciplinary expert panel.

Introduction

The incidence of esophageal cancer in the Dutch population has increased over the past three decades[1]. The European Standard Population adjusted incidence rate (ESR) for esophageal adenocarcinoma in males tripled from 3.2 per 100,000 in 1989 to 9.9 per 100.000 in 2008. In females the ESR increased from 0.7 to 1.7 per 100,000. For males no change in the incidence for esophageal squamous-cell carcinoma was observed, while females showed a slight increase[2].

According to the Dutch clinical practice guidelines, neoadjuvant chemoradiation followed by surgery is the preferred treatment for patients with locally advanced esophageal cancer. Endoscopic mucosal resection (EMR) is indicated for early cancer (T1a- lesions)[3]. Definitive chemoradiation or palliative treatment is indicated for patients with non-metastasized T4b tumors or for patients who are frail[4-7]. Due to a process of centralisation, treatment of esophageal cancer in the Netherlands is now largely performed in regional centres of referral. Within these centers of excellence, patients are discussed at multidisciplinary team (MDT) meetings and managed according to the national guidelines and latest evidence. Concentration of care for esophageal cancer patients is associated with improved peri-operative mortality and overall survival in surgically treated and non-surgically treated patients[8-11].

Most patients with esophageal cancer are diagnosed in non-referral centres. In a non-referral hospital, patients might not be discussed in a MDT proficient in all aspects of diagnosis and treatment of esophageal cancer. These hospitals thus play a crucial role in deciding whether or not a patient is referred to an expert centre for further treatment. MDT meetings for rectal and breast cancer improve surgical outcomes through better patient management[12;13]. MDT meetings for esophageal cancer improve staging accuracy and often to alter the initial treatment plan[14;15].

The aim of this study is to assess the relationship between hospital of diagnosis and referral for a curative treatment. Secondly, the referral pattern and its influence on overall survival in patients with resectable esophageal cancer was explored.

Methods

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. All patients diagnosed with a histological diagnosis of esophageal cancer between 2003 and 2010 were selected for this study (ICD-0-3: 8010, 8012, 8020, 8021, 8032, 8033, 8041, 8046, 8070-8072, 8076, 8078, 8083, 8140, 8144, 8145, 8210, 8211, 8246, 8260, 8480, 8481, 8490, 8560, 8570, 8574).

The ECR collects data on all patients with newly diagnosed cancer in the south of the Netherlands. This region comprises approximately 2.4 million inhabitants. This population-based registry includes ten hospitals, six pathology departments, and two radiotherapy institutions. Since 1999 esophageal cancer surgery has been centralized in two centres.

Information on hospital of first diagnosis, age, gender, socioeconomic status (SES), co-morbidity, histology, tumor stage (classified by the International Union Against Cancer (UICC) TNM 6[16]), tumor location (according to International Classification of Diseases for Oncology (ICD-O-3))[17], and treatment is routinely extracted from the medical records by specially trained administrators of the cancer registry. Tumor location was classified as proximal (above tracheal bifurcation, C15.0, C15.1, C15.2, and C15.3), mid (between tracheal bifurcation and gastro-esophageal junction, C15.4), distal (gastro-esophageal junction, C15.5), and overlapping or not otherwise specified (C15.8, C15.9).

Clinical tumor (cT) and lymph node (cN) stage was determined by at least endoscopy, computed tomography (CT) scanning of the chest and abdomen and ultrasound of the neck. Positron emission tomography (PET)-CT or Endoscopic ultrasound (EUS) were performed when indicated. Tumor stage recorded by the ECR was defined by pathologic examination of the resection specimen or, if not available, clinical tumor stage.

Information on medical history and co-morbidity was summarized on a modified list of the Charlson co-morbidity index[18]. Hypertension was not scored as co-morbidity given its high prevalence and minor impact on patients' health status. Individual SES, based on fiscal data on value of the home and household income, is provided at an aggregated level for each postal code[19]. Surgery with curative intent was classified according to the cancer registry as total esophagectomy, partial esophagectomy, multi-organ surgery or surgery not otherwise specified. Radiotherapy and chemotherapy were classified as yes or no. Local tumor surgery, palliative therapies in general, and palliative therapy of metastases were defined as 'other therapy'. Treatment with curative intent was defined as surgery or definitive chemoradiation. Treatment with no curative intent included radiotherapy alone, chemotherapy alone, and other therapy. Hospital of diagnosis was classified as the hospital where the clinical or pathological diagnosis of esophageal cancer was made. Hospitals of diagnosis outside the ECR region were defined as "non regional" hospitals.

Statistical analysis

Differences in patient and tumor characteristics between hospitals of diagnosis were compared using chi-square tests. Univariable and multivariable logistic regression analyses were conducted to evaluate the influence of hospital of diagnosis, age, gender, SES, co-morbidity, tumor stage, tumor differentiation, and tumor location on surgery and treatment with curative intent (surgery or definitive chemoradiation). Results were reported as odds ratios (OR) and 95% confidence intervals (95% CI). Univariable and multivariable Cox regression analyses were performed to determine the prognostic impact of hospital of diagnosis, age, gender, co-morbidity, SES, tumor location, tumor differentiation, tumor stage, surgery and definitive chemoradiation on overall survival. Survival time was defined as time from diagnosis to death or until January 1st, 2010 for the patients who were still alive. Survival results were reported as hazard ratios (HR) and 95% CI. In all analyses we used the hospital with the highest percentage of patients receiving esophageal surgery with curative intent as our reference. All analyses were performed using Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). All reported p-values below 0.05 were considered statistically significant.

Results

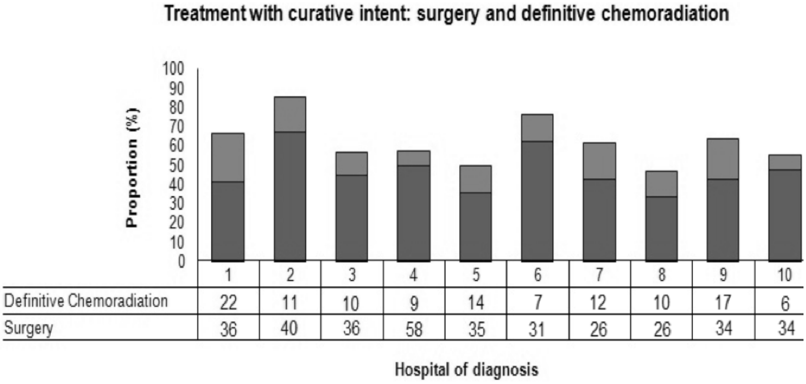
Patients

Between 2003 and 2010, 1672 patients with esophageal cancer (C15) were diagnosed in the ECR region. We excluded 533 patients with metastatic disease (UICC-TNM 6 M1b-M1) and 143 patients with tumors infiltrating surrounding organs (T4) since these patients are not always eligible for curative intent resection. Furthermore, patients with an unknown or missing M-status where excluded (n=145) and two patients with unknown therapy, resulting in a study population of 849 patients with resectable and curable esophageal cancer (T1-3, N0-1, M0-1a).

Treatment

No significant differences were observed in gender, age, co-morbidity, T-stage, histology and tumor location of the patients from the hospitals of diagnosis in the ECR region (Table 1). However, SES and N-stage were significantly different between the hospitals of diagnosis. There was a difference in the proportion of patients that underwent surgery, ranging from 33% to 67% (p=0.002). Furthermore, the proportion of patients that underwent definitive chemoradiation ranged from 8% to 25% between the hospitals of diagnosis (p=0.039) (Figure 1). 17% of all patients received chemoradiation with surgery.

Figure 1. Proportions (%) of patients with esophageal cancer receiving treatment with curative intent in 10 hospitals of diagnosis in the ECR region in the period 2003-2010 (N=849)



	1	2	3	4	5	6	7	8	9	10
Definitive Chemoradiation	22	11	10	9	14	7	12	10	17	6
Surgery	36	40	36	58	35	31	26	26	34	34

Table 1. Characteristics of patients diagnosed with resectable esophageal cancer in the ECR region in the period 2003-2010 (n=849).

		Hospital of diagnosis											
	Number of patients	1	2	3	4	5	6	7	8	9	10	11*	p-value
		88	60	81	118	99	50	62	79	81	72	59	
Gender													
Male	633	62	45	65	84	72	39	47	63	61	54	41	
Female	216	26	15	16	34	27	11	15	16	20	18	18	0.865
Age (yrs)													
<70	484	42	42	52	68	58	31	35	46	42	32	36	
≥70	365	46	18	29	50	41	19	27	33	39	40	23	0.114
Socioeconomic status[a]													
Low	204	18	13	28	19	22	9	25	28	15	16	11	
Intermediate	329	37	21	28	48	41	22	21	23	35	28	25	
High	255	29	21	17	40	30	14	12	21	27	21	23	
Institutionalised	38	3	2	3	8	4	2	2	5	2	7	0	
Unknown	23	1	3	5	3	2	3	2	2	2	0	0	0.032
Co-morbidity[b, c]													
None	271	37	25	26	36	27	24	17	28	25	24	2	
1	227	21	17	27	31	32	13	20	21	25	18	2	
2 or more	259	24	15	23	47	33	11	21	28	26	29	2	0.541
T-stage[a]													
T1	47	6	10	1	3	4	4	1	5	0	3	10	
T2	102	12	7	10	12	9	4	6	8	14	14	6	
T3	313	36	26	24	37	39	23	29	30	24	24	21	
TX/missing	387	34	16	46	66	47	19	26	36	43	31	22	0.173
N-Stage													
N0	375	36	31	27	44	38	27	24	28	47	36	37	
N1	349	38	24	41	50	44	17	30	37	26	28	14	
NX/missing	125	14	5	13	24	17	6	8	14	8	8	8	0.022
Histology[a]													
Squamous-cell carcinoma	271	31	19	22	38	39	21	17	17	26	27	14	
Adenocarcinoma	537	52	38	55	75	53	27	45	54	53	42	43	
Other	41	5	3	4	5	7	2	0	8	2	3	2	0.178
Tumor location[a]													
Proximal	52	6	1	6	10	9	2	2	4	5	3	4	
Mid	105	16	6	10	16	18	6	7	6	7	6	7	
Distal	655	63	49	61	85	68	40	51	68	65	58	47	
Overlapping/NOS[d]	37	3	4	4	7	4	2	2	1	4	5	1	0.324
Surgery													
Yes	382	36	40	36	58	35	31	26	26	34	34	26	
No	467	52	20	45	60	64	19	36	53	47	38	33	0.002
Definitive chemoradiation													
Yes	127	22	11	10	9	14	7	12	10	17	6	9	
No	722	66	49	71	109	85	43	50	69	64	66	50	0.039

[a] Groups with <5 patients were not included in the Chi-square test.

[b] Does not add up to total due to unknown/missing values n= 92

[c] Excluding hypertension

[d] Not otherwise specified

*11= patients diagnosed in extra-regional hospitals

Predictive factors for surgery

In unadjusted analyses, hospital of diagnosis, age, gender, SES, co-morbidity, cT-stage, cN-stage, histology, and tumor location all had a significant influence on the probability to receive surgery (or surgery combined with peri-operative strategies) (Table 2). After adjustment for all variables listed in table 2, the multivariable analyses showed that in four hospitals patients were significantly less likely to receive surgery compared to the reference hospital with the highest percentage of patients receiving surgery. This hospital was a referral hospital for surgical treatment. Older patients (≥70 years), patients with low SES and patients with two or more co-morbidities were less likely to receive surgery. Furthermore, patients with a cT1 tumor, positive lymph node status, a proximal tumor and those with a squamous cell carcinoma or other cancers were significantly less likely to receive surgery (Table 2).

Predictive factors for curative treatments

In the univariable analyses, hospital of diagnosis, age, gender, SES, co-morbidity, clinical T-stage, clinical N-stage, histology, and tumor location all had a significant influence on predicting curative intent treatment which was defined as surgery or definitive chemoradiation with a curative intent (Table 3). In the multivariable analysis, patients diagnosed in 8 hospitals were less likely to receive a curative treatment compared to the reference hospital in the ECR region. Older patients (≥70 years), patients with two or more co-morbidities, patients with cT1 tumors and patients with positive lymph node status were less likely to receive curative intent treatment (Table 3).

Predictors of overall survival

In the unadjusted Cox regression survival analysis, hospital of diagnosis, age, co-morbidity, SES, surgery, histology, tumor differentiation, and tumor stage all had a significant influence on overall survival (Table 4). After multivariable analysis patients diagnosed in 3 hospitals were associated with a worse overall survival compared to the reference hospital. Tumor stages III and IV were significant predictors for worse overall survival, while stage I, moderate tumor differentiation and receiving surgery or definitive chemoradiation were significant predictors for better overall survival. While age ≥70 and two or more co-morbidities, were significant determinants for receiving curative intent treatment, they were not significant predictors for overall survival (Table 4).

Table 2. Univariable and multivariable logistic regression analysis for determining predictors of surgery in patients diagnosed with resectable esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients (n=849)	Univariable analysis		Multivariable analysis	
		OR	95% CI	OR	95% CI
Hospital of diagnosis					
1	88	0.4	0.2-0.7	0.4	0.2-1.0
2	60	1.0		1.0	
3	81	0.4	0.2-0.8	0.6	0.2-1.3
4	118	0.5	0.3-0.9	0.8	0.4-1.8
5	99	0.3	0.1-0.5	0.4	0.2-0.8
6	50	0.8	0.4-1.8	0.9	0.3-2.2
7	62	0.4	0.2-0.8	0.5	0.2-1.1
8	79	0.2	0.1-0.5	0.3	0.1-0.7
9	81	0.4	0.2-0.7	0.4	0.2-0.9
10	72	0.5	0.2-0.9	0.7	0.3-1.6
11[a]	59	0.4	0.2-0.8	0.4	0.1-1.1
Age (yrs)					
<70	484	1.0		1.0	
≥70	365	0.2	0.2-0.3	0.3	0.2-0.4
Gender					
Male	633	1.0		1.0	
Female	216	0.6	0.4-0.8	1.0	0.7-1.6
Socioeconomic status					
Low	204	0.5	0.4-0.8	0.6	0.4-0.9
Intermediate	329	1.0		1.0	
High	255	1.1	0.8-1.6	1.1	0.7-1.6
Institutionalised	38	0.3	0.2-0.7	0.5	0.2-1.2
Unknown	23	1.4	0.6-3.2	1.4	0.5-3.7
Co-morbidity					
None	271	1.0		1.0	
1	227	0.6	0.4-0.8	0.7	0.5-1.0
2 or more	259	0.3	0.2-0.4	0.3	0.2-0.5
Unknown	92	0.5	0.3-0.8	0.6	0.3-1.2
Clinical T stage					
T1	47	0.6	0.3-1.0	0.4	0.2-0.8
T2	102	1.2	0.8-1.9	1.5	0.8-2.6
T3	313	1.0		1.0	
T X/missing	387	0.3	0.2-0.5	0.3	0.2-0.5
Clinical N stage					
N0	375	1.0		1.0	
N1	349	0.8	0.6-1.1	0.4	0.3-0.6
NX/missing	125	0.4	0.3-0.6	0.6	0.4-1.1
Histology					
Squamous-cell carcinoma	271	0.5	0.4-0.7	0.6	0.4-0.9
Adenocarcinoma	537	1.0		1.0	
Other	41	0.3	0.1-0.6	0.3	0.1-0.7
Tumor location					
Proximal	52	0.1	0.0-0.2	0.1	0.0-0.2
Mid	105	0.5	0.3-0.8	0.6	0.4-1.1
Distal	655	1.0		1.0	
Overlapping/ not other specified	37	0.5	0.3-1.1	0.6	0.3-1.4

[a] Diagnosis in extra-regional hospitals.

Table 3. Univariable and multivariable logistic regression analysis for determining predictors of curative intent treatment (surgery or chemoradiation) in patients diagnosed with resectable esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients (n=849)	Univariable analysis		Multivariable analysis	
		OR	95% CI	OR	95% CI
Hospital of diagnosis					
1	88	0.3	0.1-0.8	0.4	0.2-1.1
2	60	1.0		1.0	
3	81	0.2	0.1-0.5	0.3	0.1-0.7
4	118	0.2	0.1-0.5	0.3	0.1-0.8
5	99	0.2	0.1-0.4	0.2	0.1-0.5
6	50	0.6	0.2-1.5	0.6	0.2-1.8
7	62	0.3	0.1-0.7	0.3	0.1-0.8
8	79	0.1	0.1-0.3	0.1	0.1-0.4
9	81	0.3	0.1-0.7	0.3	0.1-0.9
10	72	0.2	0.1-0.5	0.3	0.1-0.7
11[a]	59	0.3	0.1-0.6	0.3	0.1-1.0
Age (yrs)					
<70	484	1.0		1.0	
≥70	365	0.2	0.2-0.3	0.3	0.2-0.4
Gender					
Male	633	1.0		1.0	
Female	216	0.7	0.5-1.0	1.1	0.7-1.7
Socioeconomic status					
Low	204	0.6	0.4-0.8	0.7	0.4-1.1
Intermediate	329	1.0		1.0	
High	255	1.2	0.9-1.7	1.3	0.8-1.9
Institutionalised	38	0.2	0.1-0.5	0.4	0.2-1.1
Unknown	23	2.1	0.8-5.9	2.6	0.8-8.2
Co-morbidity					
None	271	1.0		1.0	
1	227	0.6	0.4-0.9	0.9	0.5-1.4
2 or more	259	0.3	0.2-0.4	0.4	0.3-0.6
Unknown	92	0.4	0.3-0.7	0.5	0.2-1.2
Clinical T stage					
T1	47	0.2	0.1-0.5	0.2	0.1-0.4
T2	102	1.1	0.6-2.0	1.3	0.7-2.5
T3	313	1.0		1.0	
T X/missing	387	0.2	0.1-0.2	0.2	0.1-0.3
Clinical N stage					
N0	375	1.0		1.0	
N1	349	1.1	0.8-1.5	0.5	0.4-0.8
NX-missing	125	0.3	0.2-0-5	0.5	0.3-0.9
Histology					
Squamous-cell carcinoma	271	0.8	0.6-1.1	0.9	0.6-1.4
Adenocarcinoma	537	1.0		1.0	
Other	41	0.5	0.3-1.0	0.5	0.2-1.2
Tumor location					
Proximal	52	0.6	0.3-1.0	0.5	0.3-1.1
Mid	105	0.7	0.5-1.1	0.7	0.4-1.3
Distal	655	1.0		1.0	
Overlapping/ not other specified	37	0.6	0.3-1.1	0.6	0.3-1.4

[a] Diagnosis in extra-regional hospitals.

Table 4. Univariable and multivariable Cox proportional hazards regression analyses of overall survival for patients with esophageal cancer in the ECR region in the period 2003-2010 (n=849).

	Number of patients (n=849)	Univariable overall survival		Multivariable overall survival	
		HR[b]	95%CI	HR[b]	95% CI
Hospital of diagnosis					
1	88	2.1	1.3-3.5	1.5	0.9-2.5
2	60	1.0		1.0	
3	81	3.0	1.8-4.9	1.8	1.1-3.1
4	118	2.7	1.7-4.4	1.5	0.9-2.5
5	99	2.8	1.7-4.6	1.4	0.8-2.3
6	50	1.7	0.9-3.0	1.4	0.8-2.6
7	62	3.1	1.8-5.2	1.9	1.1-3.2
8	79	3.3	2.0-5.5	1.6	1.0-2.8
9	81	2.4	1.4-4.1	1.5	0.9-2.6
10	72	3.1	1.8-5.1	2.2	1.3-3.7
11[a]	59	1.6	0.9-2.9	1.6	0.8-3.2
Age (yrs)					
<70	484	1.0		1.0	
≥70	365	1.6	1.4-1.9	1.0	0.8-1.3
Gender					
Male	633	1.0		1.0	
Female	216	1.1	0.9-1.3	0.9	0.8-1.2
Socioeconomic status					
Low	204	1.3	1.0-1.5	1.1	0.8-1.3
Intermediate	329	1.0		1.0	
High	255	0.8	0.7-1.1	0.9	0.7-1.1
Institutionalised	38	2.0	1.3-2.9	1.3	0.9-2.0
Unknown	23	0.8	0.5-1.6	0.9	0.5-1.8
Co-morbidity					
None	271	1.0		1.0	
1	227	1.4	1.1-1.7	1.2	0.9-1.5
2 or more	259	1.6	1.3-1.9	1.0	0.8-1.3
Unknown	92	0.8	0.5-1.1	0.8	0.5-1.3
Surgery					
Yes	382	0.4	0.3-0.5	0.3	0.2-0.4
No	467	1.0		1.0	
Definitive Chemoradiation					
Yes	127	0.9	0.7-1.1	0.4	0.3-0.5
No	722	1.0		1.0	
Tumor location					
Proximal	52	1.2	0.9-1.7	0.8	0.5-1.1
Mid	105	1.2	1.0-1.6	1.1	0.8-1.5
Distal	655	1.0		1.0	
Overlapping/ not other specified	37	1.4	0.9-2.1	1.2	0.7-1.8
Histology					
Squamous-cell carcinoma	271	1.3	1.1-1.5	1.2	0.9-1.5
Adenocarcinoma	537	1.0		1.0	
Other	41	1.5	1.0-2.1	1.1	0.7-1.7
Tumor differentiation					
Good	28	0.6	0.3-1.0	0.6	0.3-1.1
Moderate	219	0.8	0.7-1.0	0.8	0.6-1.0
Poor	325	1.0		1.0	
Anaplastic	8	1.5	0.7-3.1	0.7	0.3-1.6
Unknown	269	1.0	0.8-1.2	0.7	0.6-0.9
Tumor stage					
I	110	0.5	0.3-0.7	0.4	0.2-0.6
II	214	1.0		1.0	
III	172	1.7	1.3-2.2	1.6	1.2-2.1
IV	81	3.1	2.3-4.2	2.5	1.7-3.4
Unknown	272	2.5	2.0-3.2	1.5	1.1-1.9

[a] Diagnosis in extra-regional hospitals.

[b] A higher risk of dying is denoted by a hazard ratio (HR) value >1 and a lower risk of dying by a HR value <1.

Discussion

This population-based study showed a large variation between the hospitals in the proportion of esophageal cancer patients that underwent surgery in a center of referral. Furthermore, a large variation between the referring hospitals was observed in patients that underwent definitive chemoradiation. Patients diagnosed in the majority of hospitals were less likely to receive treatment with a curative intent (surgery or definitive chemoradiation) compared to being diagnosed in the reference centre with the highest probability to receive this treatment. Since all patients are first discussed in a local non-expert MDT before referral, we hypothesize that these differences might be explained by the fact that a local MDT is less proficient in defining the best treatment options for esophageal cancer patients. The finding that patients from three referring hospitals in the ECR region had a significantly worse overall survival supports this.

Hospital volume and centralization

Hospital volume is related to mortality and survival in patients after esophagectomy[9;11]. In the Netherlands, hospitals with a medium (11-20/year) or high (≥21/year) volume of esophagectomies had a significant lower 6-month mortality and a better 3-years survival compared to hospitals with very low (1-5/year) volume. Regionalisation and centralisation to increase the hospital volume of esophageal surgery might thus decrease postoperative mortality and increase long-term survival. Centralisation of esophageal cancer surgery in the ECR region has been established since 1999, when it was decided that esophageal surgery should be performed in dedicated referral hospitals. As a consequence, 3-year overall survival rates for patients with esophageal or gastric cardia cancer who received surgical treatment significantly improved from 32% in the period before centralisation to 45% in the period of centralisation in the ECR region[8]. These results are likely not only due to better surgery, but also to better staging, patient selection and decision making due to increased expertise of the health care professionals in the referral hospitals. It has been suggested that increasing volume has not only a beneficial effect on the outcome after surgery but also on the expertise of other specialties involved in esophageal treatment, since not only surgeon volume, but also hospital volume is important. For example, the sensitivity to identify lymph node metastases by CT scan or ultrasound was significantly higher in a high volume regional centre when compared with low volume centres[20;21]. Another study has shown that experience in endoluminal ultrasound (EUS) is important. High volume EUS centres (performing more than 50 EUS per endoscopist) had better results in staging compared with low volume centres[22].

Predictors for treatment

Factors that influenced the probability to receive curative treatment were hospital of diagnosis age, SES, co-morbidity, clinical T-stage, clinical N-stage, histology, and tumor location. Elderly patients and patients with multiple co-morbidities were less likely to receive surgery, results that are in concordance with others[23;24]. Low SES was a significant predictor for not receiving surgery. Previous Dutch studies also showed that patients with a higher SES were more likely to receive surgery[25;26]. Patients with squamous-cell carcinoma were less likely to receive surgery, which is in concordance with a recent study from the United States[27]. Patients with proximal tumors received surgery less often. A possible explanantion is that most proximal tumors are primarily treated with definitive chemoradiation, as advocated by the Dutch guidelines[3]. In our study cT-stage and cN-stage influenced receiving surgery, which is supported by a study that showed an influence of cT-stage and cN-stage on disease-free, disease-specific, and overall survival[28]. Patients with cT1 tumors were less likely to undergo surgical treatment. This is probably caused by the systematic introduction of the EMR in the ECR region during the study period. Age, gender, SES, co-morbidity, clinical T-stage, clinical N-stage, histology, and tumor location all influenced the probability to receive curative treatment. However, since most of these factors were not significantly different between the hospitals of diagnosis and hospital of diagnosis was the most powerful independent predictor to receive curative treatment, other factors might influence the decision whether or not to refer patients for curative treatment.

In our study only 144 patients (17%) were offered chemoradiation and surgery according to the Dutch guidelines, which is probably due to the fact that our study has started in 2003 and randomized trials studying neoadjuvant chemoradiation like the CROSS trial were still ongoing[29].

In the ECR region, the referring hospital's MDT includes physicians with a vast experience in oncological decision making. However, the palliative and curative treatment options for esophageal cancer patients has become more complex and new developments diffuse rapidly. This might explain the differences in the proportion of patients receiving curative treatment between hospitals.

Multidisciplinary team meetings

Specialised MDT meetings have shown to improve outcome in other solid tumors like rectal and breast cancer. The implementation of expert based MDT meetings in rectal cancer has resulted in a major improvement of surgical outcome with a reduction in positive resection margins (CRM+) from 26% to only 1%.[12] MDT meetings in breast cancer have shown to lead to changes in recommendations for surgical management in 52% of the cases[13]. In esophageal cancer, a recent study has shown that in 35% of the cases the initially proposed management plan by the referring hospital was altered after the MDT meeting even within a referral centre[15]. Furthermore, due to the interaction between disciplines, MDT meetings have been shown to improve staging accuracy of esophageal cancer, which ensures correct management decisions[14].

These studies support the concept of regional tumor board meetings to increase the probability of receiving a curative treatment. This could be organised by referring all patients with esophageal cancer to an expert centre for further staging and decision making or to organize a regional diagnosis based expert MDT meeting in every hospital by means of expert consultation or video conferencing. Since hospital of diagnosis also influenced the probability of survival, implementation of these processes might improve survival of patients with esophageal cancer. After multivariable analysis the differences in survival between the hospitals are decreasing, probably by correction for treatment. For patients with esophageal cancer who are not eligible for surgery due to co-morbidities or irresectable/inoperable tumors, definitive chemoradiation is a well tolerated option with encouraging survival rates[5;6]. Furthermore, two important clinical trials in patients with squamous cell carcinoma showed that good responders on chemoradiation alone versus chemoradiation with surgery have comparable survival rates[30;31]. Thus, definitive chemoradiation is a reasonable alternative curative option, especially in patients with squamous-cell carcinoma. In our multivariate analysis hospital of diagnosis also influenced the proportion of patient offered definitive chemoradiation, suggesting that there is a significant difference of knowledge of the palliative and curative possibilities of definitive chemoradiation.

Limitations

A strength of the present study is that the ECR collects data on comorbidity and that we could correct for most factors that could influence decision-making in the multivariable analysis. This study also has its limitations. We excluded patients with distant metastasis (M1). Furthermore we excluded all T4 tumors, since it was not possible to identify T4 tumors which might still be eligible for surgery with or without neo-adjuvant treatment. How accurate clinical staging was is unknown. At least endoscopy, CT scan and an ultrasound of the cervical region was performed in all patients. Since EUS was not performed in all patients, a relatively high number of missing T (n=387) and N stages (n=125) were identified. However, in determining resectability of esophageal cancer, an EUS is not accurate[32]. The use of PET/CT as the first staging procedure with reserving EUS for cases with uncertainty about positive lymph nodes or tumor depth is sufficient.

In conclusion, hospital of diagnosis plays a significant role on the probability to receive potentially curative treatment and overall survival in patients with resectable esophageal cancer in the southern part of the Netherlands. All patients diagnosed with esophageal cancer should be discussed within a regional multidisciplinary expert panel.

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CHAPTER 5

Hospital of diagnosis influences the probability of receiving curative treatment for esophageal cancer

Authors:

Margreet van Putten [1]; Marijn Koëter MD[2]; Hanneke W.M. van Laarhoven MD, PhD[3];
Valery E.P.P. Lemmens PhD[1,4]; P.D. Siersema MD, PhD[5];
Maarten C.C.M. Hulshof MD, PhD[6]; Rob H.A. Verhoeven PhD[1];
Grard A.P. Nieuwenhuijzen MD, PhD[2]

Affiliation:

[1] Department of Research,
Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands.

[2] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands.

[3] Department of Medical Oncology,
Academic Medical Center of Amsterdam, The Netherlands

[4] Department of Public Health,
Erasmus MC - University Medical Centre Rotterdam, The Netherlands

[5] Department of Gastroenterology and Hepatology,
Radboud University Medical Center, Nijmegen, The Netherlands

[6] Department of Radiotherapy,
Academic Medical Center of Amsterdam, The Netherlands

Abstract

Background: Although Esophageal Cancer (EC) surgery is centralized in the Netherlands, the disease is often diagnosed in hospitals which do not perform this procedure. To study the influence of hospital of diagnosis on the probability of receiving curative treatment and its impact on survival among patients with esophageal cancer.

Material and method: Patients with potentially curable esophageal or gastro-esophageal junction tumors diagnosed between 2005 and 2013 who were potentially curable (cT1-3,X, any N, M0,X) were selected from the Netherlands Cancer Registry. Multilevel logistic regression was performed to examine the probability to undergo curative treatment (resection with or without neoadjuvant treatment, definitive chemoradiotherapy or local tumor excision) according to hospital of diagnosis. Effects of variation in probability of undergoing curative treatment among these hospitals on survival were investigated by Cox regression.

Results: All 13,017 patients with potentially curable EC, diagnosed in 91 hospitals, were included. The proportion of patients receiving curative treatment ranged from 37% to 83% and from 45% to 86% in the periods 2005-2009 and 2010-2013, respectively, depending on hospital of diagnosis. After adjustment for patient- and hospital-related characteristics these proportions ranged from 41% to 77% and from 50% to 82%, respectively (both $P<0.001$). Multivariable survival analyses showed that patients diagnosed in hospitals with a low probability of undergoing curative treatment had a worse overall survival (HR=1.13 95%CI 1.06-1.20;HR=1.15; 95%CI 1.07-1.24).

Conclusion: The variation in probability of undergoing potentially curative treatment for EC between hospitals of diagnosis and its impact on survival indicates that treatment decision-making in EC may be improved.

Introduction

Esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related mortality worldwide[1]. The incidence of esophageal cancer in the Western world has risen over the past four decades and is still rising but at a slower rate than previously observed[2,3]. Although survival rates have improved during the past decade, they still remain poor with a 5-year relative survival ranging from 19%-25% for patients with M0 esophageal cancer and a 2-year relative survival of 9% for M1 esophageal cancer[4,5].

Esophagectomy with neo-adjuvant chemoradiotherapy is the most commonly used curative treatment modality for patients with locally advanced esophageal cancer[6,7]. Other curative treatment options include definitive chemoradiotherapy (dCRT) for non-metastasized patients with unresectable tumors or patients who are too frail to undergo surgery[8-10], whereas endoscopic mucosal resection (EMR) is indicated for early stage esophageal cancer (T1a-lesions)[11,12]. For esophageal cancer patients with distant metastasis at diagnosis (40%), treatment with curative intent is no longer an option[12]. Similarly, curative treatment should be withheld when patients are too frail, have severe comorbidities or a reduced performance status[13].

Previous nationwide studies have shown that the probability of undergoing curative treatment for gastric or pancreatic cancer is associated with hospital of diagnosis[14,15]. Referring physicians may have several reasons to consider the patient to be unsuitable for surgery and withhold possible curative options. Furthermore, a regional Dutch study showed that among potentially curable esophageal cancer patients the percentage of patients undergoing surgical treatment varied between 33% and 67% according to hospital of diagnosis[16]. These results were however based on data from eleven general hospitals in the South of the Netherlands, with only two of them being centers for esophageal cancer surgery.

Both surgical treatment of esophageal cancer and endoscopic mucosal resection for early cancer are nowadays centralized, but the initial decision which treatment modality to perform, including the decision whether or not to refer patients for a curative treatment option is made in all Dutch hospitals. Therefore, it is important to evaluate the impact of hospital of diagnosis on the referral pattern for curative treatment and ultimately survival. The aim of this study was to examine the influence of the hospital of diagnosis on the probability to undergo a curative treatment option for esophageal cancer in the Netherlands. Furthermore, the association between the variation in curative treatment probability among hospitals of diagnosis and overall survival was assessed.

Methods

Netherlands cancer registry

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is 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, hematology departments, radiotherapy institutions and diagnosis therapy combinations (specific codes for reimbursement purposes). Specially trained data managers of the NCR routinely extracted information on diagnosis, tumor stage and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered.

Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3)[17], in which subsite distribution is divided as: proximal (C15.0, C15.3), mid (C15.4), distal (C15.5), overlapping or not otherwise specified (C15.8, C15.9) and gastro-esophageal junction (GEJ) (C16.0). Tumor staging was performed according to the International Union Against Cancer (UICC) TNM classification that was valid at the time of diagnosis. Patients diagnosed between 2005 and 2009 were staged according to TNM-6 and patients diagnosed between 2010 and 2013 were staged according to TNM-7[18,19]. Patients with GEJ cancer diagnosed between 2005 and 2009 were staged according to the TNM-6 classification for gastric and after 2010 according to the TNM-7 classification for esophageal cancer. Clinical tumor stage was assessed for the inclusion of patients and used in the multilevel logistic regression analyses. For survival analyses, the pathologic reports of the resection specimen were assessed, or, if not available, clinical tumor stage was noted. Patients with a potentially curable esophageal and GEJ cancer (cT1-3,X, any N, M0,X) were eligible for this study (Figure 1). Patients were considered to be potentially curable in this study if they had no clinically distant metastasis (cM0 and cM1a according to TNM-6 and cM0 according to TNM-7) and no tumor infiltrating into surrounding organs (no cT4 according to TNM-6 and no cT4A or cT4b according to TNM-7). For the analyses, patients with a cM1a tumor according to TNM-6 were categorized as having cN+ as most patients with a cM1a tumor had a distal tumor with coeliac lymph nodes which can be considered as having cN+ according to TNM-7. Furthermore, patients with unknown clinical distant metastases (cMX) were included. It should be noted that as of 2010 coding regulations to register a cM0 or cM1 status into the NCR were less strict than prior to 2010, and therefore as of 2010 relatively more patients were registered with a cM0 rather than a cMX into the NCR._To account for this, we decided to include all patients with cMX.

Curative treatment

Curative treatment was defined as surgical resection, dCRT or a local tumor excision in potentially curable patients with cT1-3,X, any N, M0,X disease. A surgical resection could be combined with or without (neo)adjuvant therapy. dCRT was defined as undergoing chemotherapy combined with radiotherapy without a surgical resection. A local tumor excision was defined as having a local tumor excision or an EMR.

Hospital of diagnosis

As the focus of this study was the decision-making process, the hospital of diagnosis was investigated rather than the hospital of resection. Hospital of diagnosis was defined as the hospital of histological confirmation for patients with a histological confirmation of the tumor (98%). If patients only had a clinical diagnosis, the hospital of diagnosis was defined as the hospital of clinical diagnosis. Patients were excluded from the study if esophageal cancer was diagnosed abroad. In the Netherlands, patients are diagnosed with esophageal cancer in any of the 91 hospitals, usually the one closest to the patient's place of residence. If the hospital of diagnosis does not perform esophageal cancer surgery or EMR, patients should be referred to an expert center when these treatments are indicated.

The experience of the hospital in performing esophageal cancer surgery was divided in two categories: Those that performed at least twenty resections per year and those with a lower annual volume, according to the year of diagnosis. For example, if a patient was diagnosed in 2011 in a hospital that performed twenty or more resections in 2011, the patient was included in the group of hospitals with an annual resection volume of at least twenty procedures.

Outcome measures

Curative treatment probability and overall survival were the primary outcomes investigated in this study. The curative treatment probability was defined as the proportion of patients diagnosed in a hospital who eventually underwent surgical resection, dCRT or local tumor excision, regardless of the hospital in which those treatments were undertaken. Survival time was defined as time from diagnosis to death or until February 1st 2016 for patients who were still alive.

Statistical analysis

Multilevel logistic regression analyses were used to analyze the hierarchically structured data as patients were nested within hospitals. These analyses provide more accurate estimates when dealing with hierarchically structured data than traditional logistic regression analyses since it accounts for dependency of patients within hospitals[20,21]. The outcome variable was curative treatment probability. Multilevel logistic regression models were performed for the periods

2005-2009 and 2010-2013 as the entire study period included centralization of esophageal cancer surgery and two new treatment paradigms: the introduction of neoadjuvant chemoradiotherapy and the introduction of EMR. The multivariate multilevel regression models were generated, and patient-, tumor-, and hospital-related variables were added. The effect of a variable on the likelihood of curative treatment was expressed as an odds ratio (OR) with 95% confidence intervals (CI). Each patient's adjusted likelihood of undergoing curative treatment was given by the following formula: $P = e^L / (1+e^L)$ where L is the calculated value from the logistic regression for that particular patient. The mean adjusted curative treatment probability for each hospital of diagnosis was obtained by calculating the mean adjusted curative treatment probability of all patients diagnosed within a hospital adjusted for differences in patient- and tumor characteristics between hospitals. Differences between probabilities for hospitals were tested for statistical significance by means of ANOVA with Bonferroni correction. Information on co-morbidity and socioeconomic status was not routinely collected by the NCR but only in a sub-cohort, i.e. the Eindhoven Cancer Registry, which is also part of the NCR. Therefore, a similar analysis was performed in the group of patients within the Eindhoven Cancer Registry to examine the influence of co-morbidity and socio-economic status on the probabilities to undergo curative treatment depending on the hospital of diagnosis.

Multivariable Cox regression analyses were performed to investigate the impact of the variation in curative treatment probability among the hospitals of diagnosis on the overall survival of the patients, after adjustment for patient-, tumor- and hospital-related characteristics. The hospitals of diagnosis, including the patients, were clustered into three groups with a similar number of patients according to the adjusted probability to undergo curative treatment within a hospital. Two multivariable cox regression analyses were performed to investigate the prognostic impact of the variation separately for the periods 2005-2009 and 2010-2013. Calculation of the curative treatment probabilities of the hospitals in the entire study period would not provide an accurate estimate and so hospitals, and thus patients, could be categorized erroneous. Results from survival analyses using Cox regression analyses were reported as hazard ratios (HRs) and 95% CI. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Caroline, USA) and reported *P* values of <0.050 were considered statistically significant.

Results

Patients

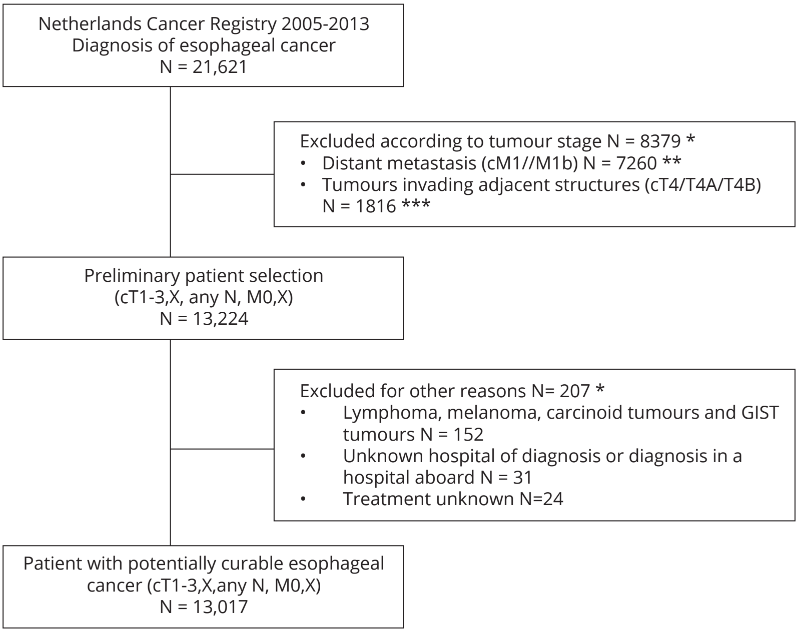
Between January 2005 and December 2013, 21,621 patients were diagnosed with esophageal or GEJ cancer. Exclusion of patients (Figure 1) resulted ultimately in a study population of 13,017 patients with potentially curable esophageal or GEJ cancer (cT1-3,X, any N, M0,X). General characteristics of the patients are shown in table 1. The median age was 69 (IQR 61-78) years and the majority (73%) of the patients were male.

Curative treatment

The curative treatment rate was 57% (N=3950) in the period 2005-2009, of which 44% underwent surgery, 9% received dCRT and 4% underwent a local tumor excision. In the period 2011-2013, the curative treatment rate was higher; 68% (N=4162), of which 46% undergoing surgery, 16% received dCRT and 6% underwent a local tumor excision (Table 1).

Patients were diagnosed with esophageal cancer in 91 hospitals. Twenty of these hospitals performed at least twenty esophageal resections in 2013, whereas in 2005 only two hospitals had a volume of twenty or more resections. The hospitals which performed in 2013 at least twenty resections comprised both academic and teaching hospitals. Surgery was not performed in 33 hospitals in 2005, which increased to 66 hospitals in 2013. Furthermore, 42% of the patients (N=224) diagnosed in 2005 and who underwent a resection was referred to another hospital for surgery, whereas 67% of the patients (N=464) diagnosed in 2013 and who underwent a resection were referred to another hospital for surgery in 2013.

Figure 1: Study flowchart



* The sum of the excluded patients per exclusion criteria is larger than the total number of excluded patients because some patients met two exclusion criteria.

** cM1B according to TNM-6 and cM1 according to TNM-7.
Patients with a cM1A tumor were categorized as having a cN+ tumor.

*** cT4 according to TNM-6 and cT4A and cT4B according to TNM-7.

Table 1. Characteristics and differences in curative treatment among patients with potentially curable esophageal cancer (cT1-3,X,any N, M0,X), diagnosed between 2005 and 2013 in the Netherlands (N=13,017)

	Number of patients	%*	Surgical treatment rate (%)**	dCRT rate (%)**	Local tumor-excision (%)**	Curative treatment rate (%)**	*P* ***
All patients	13017	100%	45%	12%	5%	62%	
Gender							<0.001
Male	9486	73%	48%	12%	5%	66%	
Female	3531	27%	37%	12%	4%	53%	
Age (years.)							<0.001
< 60	2820	22%	66%	12%	5%	83%	
60-74	5751	44%	56%	14%	5%	76%	
≥ 75	4446	34%	17%	9%	5%	31%	
Interval of diagnosis							<0.001
2005-2009	6915	53%	44%	9%	4%	57%	
2010-2013	6102	47%	46%	16%	6%	68%	
Tumor location							<0.001
Proximal	659	5%	9%	42%	2%	53%	
Mid	1608	12%	34%	18%	4%	55%	
Distal	7639	59%	48%	11%	6%	66%	
GEJ	2550	20%	55%	5%	2%	62%	
Overlapping, unknown	561	4%	28%	14%	5%	47%	
Morphology							<0.001
Squamous cell carcinoma	3185	24%	32%	23%	2%	57%	
Adenocarcinoma	9211	71%	52%	8%	6%	66%	
Other	621	5%	15%	13%	2%	31%	
cT classification							<0.001
T1	844	6%	37%	5%	36%	78%	
T2	2378	18%	59%	14%	<1%	73%	
T3	5243	40%	61%	17%	<1%	79%	
TX	4552	35%	21%	7%	7%	35%	
cN classification							<0.001
N0	4492	35%	52%	11%	8%	71%	
N+	6165	47%	51%	17%	<1%	68%	
NX	2360	18%	15%	3%	13%	31%	
cM classification							<0.001
M0	11550	89%	49%	13%	5%	67%	
MX	1467	11%	16%	5%	8%	28%	
Number of esophageal cancer resections in hospital of diagnosis							<0.001
<20	10520	81%	45%	12%	4%	61%	
≥20	2497	19%	45%	14%	11%	70%	

dCRT= definitive chemoradiotherapy, *column percentage **row percentage. *** X^2 test based on curative treatment rate. GEJ= gastro-esophageal junction

Hospital of diagnosis and probability of curative treatment

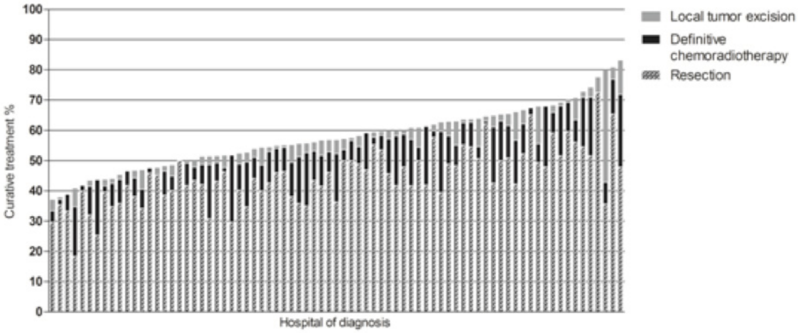
The unadjusted percentage of patients who underwent a curative treatment differed significantly between hospitals of diagnosis in the period 2005-2009, varying from 37% to 83% (Figure 2a; P <0.001), and in the period 2010-2013 from 45% to 86% (Figure 2b; p<0.001). In the most recent period, the proportion of patients who underwent surgery varied from 21% to 71%, while the percentage of patients receiving dCRT or local tumor resection varied from 0% to 38% and 0% to 31%, respectively.

Multivariate multilevel analysis confirmed the effect of hospital of diagnosis on the probability to undergo curative treatment. After adjustment for patient-, tumor- and hospital- related factors, curative treatment rates ranged from 41% to 77% in the period 2005-2009 and from 50% to 82% in the period 2010-2013 depending on the hospital of diagnosis (both P <0.001; Figure 3a and 3b). Subgroup analysis of patients within the Eindhoven Cancer Registry showed that, after adjustment for comorbidity and socio-economic status, the mean probability to undergo curative treatment per hospital of diagnosis only changed by 0.1% to 1.5% compared with results from analyses without comorbidity and socio-economic status. Additional analyses based on outcomes of the multilevel analyses showed that patients diagnosed in nine hospitals had a significant higher probability to undergo curative treatment than the average probability of all hospitals in the period 2010-2013, while patients diagnosed in six other hospitals had a significant lower probability than the average probability of all hospitals (Supplementary figure 1).

Results of the multivariate multilevel analysis showed that being diagnosed in a hospital that performed twenty or more resections per year was associated with a higher probability of undergoing curative treatment compared to being diagnosed in hospitals with less than twenty resections in the earlier period (OR 1.54; 95%CI 1.19-1.98) (Table 2). However, in the recent period this association was no longer found. In figure 3a and 3b, hospitals which performed 20 or more resections in 2009 and 2013 respectively, were highlighted.

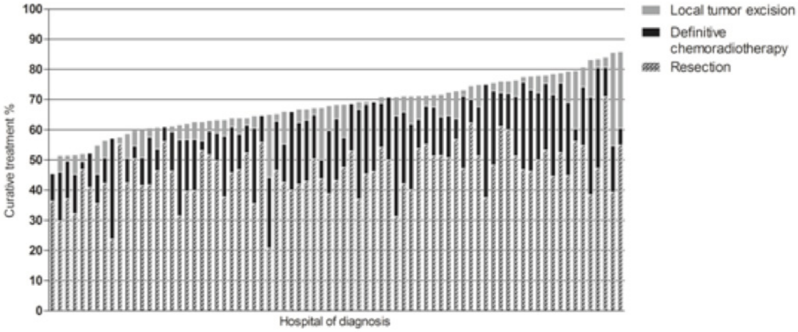
Figure 2. Observed variation in the proportion of patients with potentially curable esophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumor excision).

Figure 2A.



Period 2005-2009 (N=6915, P<0.01). Each bar represents one hospital.

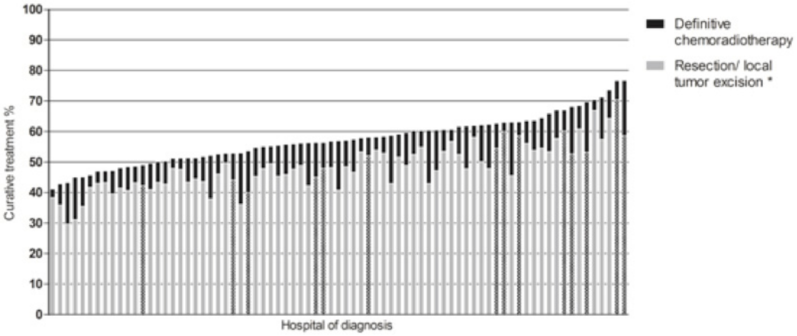
Figure 2B.



Period 2010-2013 (N=6102, P<0.01). Each bar represents one hospital.

Figure 3. Case-mix adjusted variation in the proportion of patients with potentially curable esophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumor excision) after adjustment for gender, age, cT classification, cN classification, tumor location, morphology, period of diagnosis and number of esophageal resections in the hospital of diagnosis.

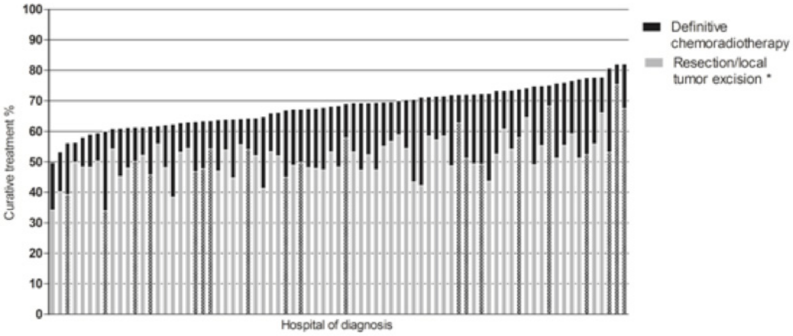
Figure 3A.



Period 2005-2009 (N=6915, P<0.01). Each bar represents one hospital and hospitals which performed 20 or more resections in 2009 and 2013.

*Patients who underwent a surgical resection or local tumor excision were combined as the multilevel logistic model provided inaccurate results as the number of patients who underwent a local tumor excision per hospital of diagnosis was too small.

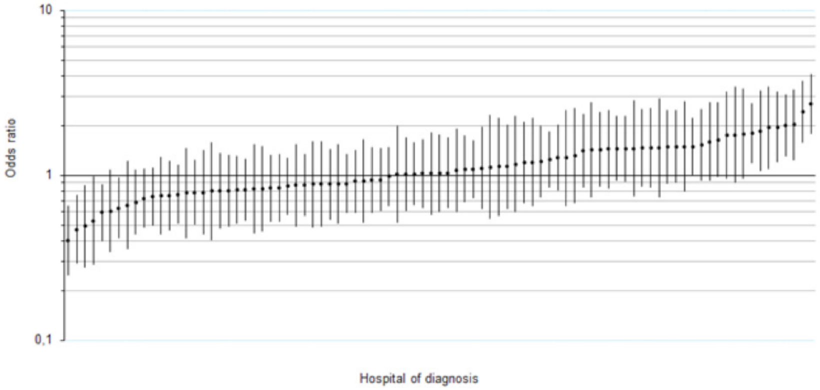
Figure 3B.



Period 2010-2013 (N=6102, P<0.01). Each bar represents one hospital and hospitals which performed 20 or more resections in 2009 and 2013.

*Patients who underwent a surgical resection or local tumor excision were combined as the multilevel logistic model provided inaccurate results as the number of patients who underwent a local tumor excision per hospital of diagnosis was too small.

Supplementary Figure 1. Case-mix adjusted variation in the proportion of patients with potentially curable esophageal cancer (cT1-3,X,any N, M0,X) who underwent a curative treatment (resection, definitive chemoradiotherapy or local tumor excision) in the period 2010-2013 on a log scale with an odds ratio for every hospital of diagnosis presented as a dot with 95% confidence interval. The 1-line represents the average probability of all hospitals. Patients diagnosed in hospitals with an odds ratio less than 1 had a lower likelihood to undergo curative treatment. Adjustment was made for gender, age, cT classification, cN classification, tumor location, morphology, period of diagnosis and number of esophageal resections in the hospital of diagnosis (N=6102).



Hospital of diagnosis and overall survival

Multivariable Cox regression analyses showed that patients diagnosed in hospitals with a lower probability of undergoing curative treatment had a worse overall survival than those diagnosed in hospitals with a higher probability. In the recent time period patients diagnosed in hospitals with a probability to undergo curative treatment ranging from 72% to 82% had a significant favorable overall survival compared to patients diagnosed in hospitals with a lower probability ranging from 50% to 64% (HR=1.15 95%CI 1.07-1.24; Table 3). A similar association was also found in the earlier time period (HR=1.13 95%CI 1.06-1.20). Furthermore, the same multivariable cox regression analyses demonstrated that patients diagnosed in high-volume surgery hospitals had a favorable survival compared to patients diagnosed in low-volume surgery hospitals (HR=0.90 95%CI 0.83-0.98). However, this association was not found in the recent time period (HR=0.99 95%CI 0.93-1.08).

Table 2. Multivariate multilevel logistic regression analyses to examine predictors of curative treatment in patients diagnosed with potentially curable esophageal cancer in the Netherlands.

	Period 2005-2009 N=6915				Period 2010-2013 N=6102			
	Curative treatment				Curative treatment			
	Yes	No	OR*	95%CI	Yes	No	OR*	95%CI
Gender								
Male	3043	1965	1.0		3210	1268	1.0	
Female	907	1000	0.87	0.75-0.99	952	672	0.80	0.68-0.94
Age (yrs.)								
< 60	1250	324	1.0		1097	149	1.0	
60- 74	2075	835	0.64	0.57-0.78	2303	538	0.62	0.50-0.76
≥ 75	625	1806	0.10	0.08-0.12	762	1253	0.10	0.08-0.13
cT classification								
T1	301	109	1.05	0.77-1.42	356	78	1.43	1.04-1.97
T2	802	318	1.0		936	322	1.0	
T3	1855	638	1.17	0.97-1.41	2266	484	1.57	1.30-1.89
TX	992	1900	0.28	0.23-0.33	604	1056	0.29	0.24-0.35
cN classification								
N0	1583	710	1.0		1606	593	1.0	
N+	1934	1192	0.38	0.33-0.45	2253	786	0.64	0.55-0.76
NX	433	1063	0.31	0.26-0.37	303	561	0.38	0.30-0.47
Tumor location								
Proximal	169	183	0.98	0.73-1.30	179	128	0.73	0.53-0.99
Mid	414	423	0.91	0.74-1.11	476	295	0.89	0.70-1.12
Distal	2389	1612	1.0		2638	1000	1.0	
GEJ	870	565	1.47	1.25-1.73	716	399	0.67	0.56-0.80
Overlapping, unknown	108	182	0.62	0.45-0.85	153	118	0.65	0.47-0.89
Morphology								
Squamous cell	882	788	0.67	0.56-0.79	944	571	0.57	0.47-0.70
Adenocarcinoma	2972	1897	1.0		3123	1219	1.0	
Other	96	280	0.34	0.25-0.46	95	150	0.37	0.26-0.53
Number of esophageal cancer resections in hospital of diagnosis								
<20 resections	3334	2671	1.0.		3031	1484	1.0	
≥20 resections	616	294	1.54	1.19-1.98	1131	456	1.08	0.82-1.42

* Adjusted for all variables listed in table 2 and hospital of diagnosis by using multilevel analysis.
GEJ= gastro-esophageal junction

Table 3. Multivariable Cox proportional hazards analyses of overall survival for patients with potentially curable esophageal cancer in the Netherlands for two separated periods of diagnosis.

	Number of patients	Crude 2-year OS [a]	Univariable HR [a]	95%CI	Multivariable HR [a] *	95% CI
2005-2009 (n=6915)						
Curative treatment probability **						
41%-53%	2261	32%	1.28	1.20-1.36	1.13	1.06-1.20
54%-59%	2128	33%	1.18	1.11-1.26	1.10	1.03-1.17
60%-77%	2526	42%	1.0		1.0	
2010-2013 (n=6102)						
Curative treatment probability **						
50%-64%	2308	40%	1.26	1.18-1.36	1.15	1.07-1.24
65%-71%	1711	47%	1.13	1.04-1.22	1.05	0.96-1.14
72%-82%	2083	50%	1.0		1.0	

[a] OS= overall survival.

* Adjusted for gender, age, tumors stage, tumors location, morphology, tumor differentiation and number of esophageal cancer resections in hospital of diagnosis.

** Patients were divided in three groups with a similar number of patients according to the adjusted probability to undergo curative treatment of the hospital in which they were diagnosed.

Discussion

In this population-based nationwide study the proportion of esophageal cancer patients who underwent curative treatment (surgery, dCRT or local tumor excision) varied between 37% and 83% in the period 2005-2009 and between 45% and 86% in the period 2010-2013. Multivariate multilevel regression analysis confirmed the effect of hospital of diagnosis on the likelihood to undergo curative treatment. Patients with esophageal cancer who had been diagnosed in hospitals with a low probability to undergo curative treatment had a worse overall survival than those diagnosed in hospitals with a high probability.

Hospital variation and treatment probability

Our results show that the differences between hospitals in the proportion of patients that underwent dCRT were larger than the differences in the proportion of patients that underwent surgery. An explanation may be that dCRT has only recently been introduced. Therefore, increased awareness of the possibilities of chemoradiation combined with favorable results reported by previous studies might have played a role in the implementation of dCRT as a potential curative option[22,23]. Furthermore, this variation might also be explained by the fact that the indications for dCRT are less well defined compared to the indications for surgery.

In previous studies it has been suggested that co-morbidity and socioeconomic status play a role in the probability of undergoing curative treatment[13, 24]. However, subgroup analysis of patients diagnosed in the Eindhoven Cancer Registry, in which co-morbidity is registered, revealed only small changes in the probability of curative treatment after adjustment for co-morbidity and socio-economic status. These findings suggest that co-morbidity and socio-economic status only minimally contributed to the observed variation in curative treatment probability between the hospitals of diagnosis.

Centralization, specialization and MDT meetings

In the Netherlands, esophageal cancer surgery is currently performed in high volume hospitals. Since 2006, a yearly minimum of ten esophageal resections per hospital was enforced by the Dutch Health Care Inspectorate, which was increased to a yearly minimum of twenty esophageal resections per hospital in 2011. Centralization of surgical treatment for esophageal cancer patients has shown to improve long-term outcome in the Netherlands[24-27]. Results from the present study showed that the number of patient that are referred by the hospital of diagnosis for surgery increased during the study period which is likely related to the centralization of surgical treatment for esophageal cancer patients. These changes due to centralization emphasize the important role of the hospital of diagnosis on the likelihood to undergo a curative treatment. The probability to undergo curative treatment may be influenced by various factors, such as type of hospital and its facilities, e.g. the availability of radiotherapy, endoscopy, regional agreements, and treatment protocols that are used. In general, all hospitals in the Netherlands have at least an endoscopy unit and radiology department, including CT scan for optimal staging. The probability of receiving curative treatment may also be affected by the available specialization of the hospital and medical specialists. Two previous studies have reported that patients treated by medical specialists with higher caseload were more likely to undergo surgery or other treatments compared to patients treated by medical specialists with a limited caseload[28,29]. Higher-volume medical specialists also used a wider range of diagnostic investigations, which was not only explained by a better access to these facilities[28]. Possibly, patients with potentially curable disease managed by low-volume medical specialists regarded incurable, could be regarded still curable by a more experienced physician because this physician may be more aware of the curative treatment possibilities[29]. The present study also shows that patients diagnosed in high-volume surgery hospitals had a greater likelihood of undergoing surgery and a better overall survival than those diagnosed in low-volume surgery hospitals. However, these associations were only found in the earlier period in which centralization of surgery was initiated. All esophageal cancer patients should be discussed in a multidisciplinary team (MDT) meeting for a consensus-based treatment decision in the Netherlands. Regional expert MDT meetings have been shown to alter initial treatment plans frequently in patients with esophageal, gastric, colorectal and breast cancer[30-34]. However, no information is available as to whether a medical specialist with experience in curative treatment of esophageal cancer is always present in this MDT. Regional MDT meetings become even more important when treatment decisions are complex as in esophageal cancer and it might be hypothesized that the presence of experienced specialists in these MDT meetings might explain differences between hospitals in the proportion of patients undergoing curative treatment.

Survival

The variation in the probability of curative treatment among hospitals of diagnosis was found to be associated with survival in both time periods. A similar study performed by the same lead author among patients with gastric cancer has also found that variation in the likelihood to undergo surgery was associated with survival.[15] However, this study has only found an association in the more recent time period. An explanation for the differences in findings of these studies could be that centralization of gastric cancer surgery has only been implemented since 2012, which is six years later than the implementation of centralization of esophageal cancer surgery. Centralization of surgery could have led to a decrease in the number of medical specialists with experience in curative treatment options for esophageal and gastric cancer patients in hospitals of diagnosis which have no longer a program for these curative treatment options. This negative consequence of centralization may have influenced the selection of patients who are eligible for curative treatment and subsequently the referral and survival of these patients among hospitals of diagnosis.

Strengths and limitations

This study has some limitations. First, some factors influencing treatment, such as performance status of the patient and information about MDT meetings decisions, were not registered and could therefore not be included in the analyses. Second, possible incompleteness of registration of local tumor excision in the earlier period could have led to more variation in curative treatment probability between hospitals in the earlier period compared to the recent period. Third, information about the intention of the chemoradiotherapy was not available. However, as only potentially curable esophageal cancer patients were included it was assumed that these patients underwent chemoradiotherapy with curative intention.

Finally, patients with distant metastasis (cM1) and cT4 tumors were excluded from the study. However, the accuracy of the diagnostic and staging methods used is unknown. Because endoscopic ultrasonography is not always performed in patients with esophageal cancer, clinical stage was unknown in a relatively high percentage of patients (Table 1). Nevertheless, the variation in cT, cN status and cM status between hospitals was much smaller than the inter-hospital variation in curative treatment probabilities and is therefore unlikely to have influenced the results substantially. Moreover, clinical decision-making in esophageal cancer treatment is more often based on cN and cM rather than on cT status [35] and it is assumed that most of the patients with a cMX prior to 2010 had in fact a cM0 as the percentage of patients with a cM0 increased after 2010 when fewer diagnostic procedures were required to register a cM0 or cM1 according to the coding regulations of the NCR. This study has also several strengths, such as its population-based design resulting in a large and representative study population. This nationwide study enabled the evaluation of the influence of the hospital of diagnosis on the probability to undergo curative treatment and its impact on survival among patients with esophageal cancer.

Conclusions

This study revealed a large variation in the probability to undergo curative treatment for esophageal cancer depending on the hospitals of diagnosis, which also affected the survival of these patients. Regional expert MDT meetings with involvement of experienced specialists in this field should be initiated for all patients with esophageal cancer. The decisions made by these panels may improve the selection of patients with esophageal cancer who are eligible for a curative treatment option leading to an overall improvement of survival on the long term.

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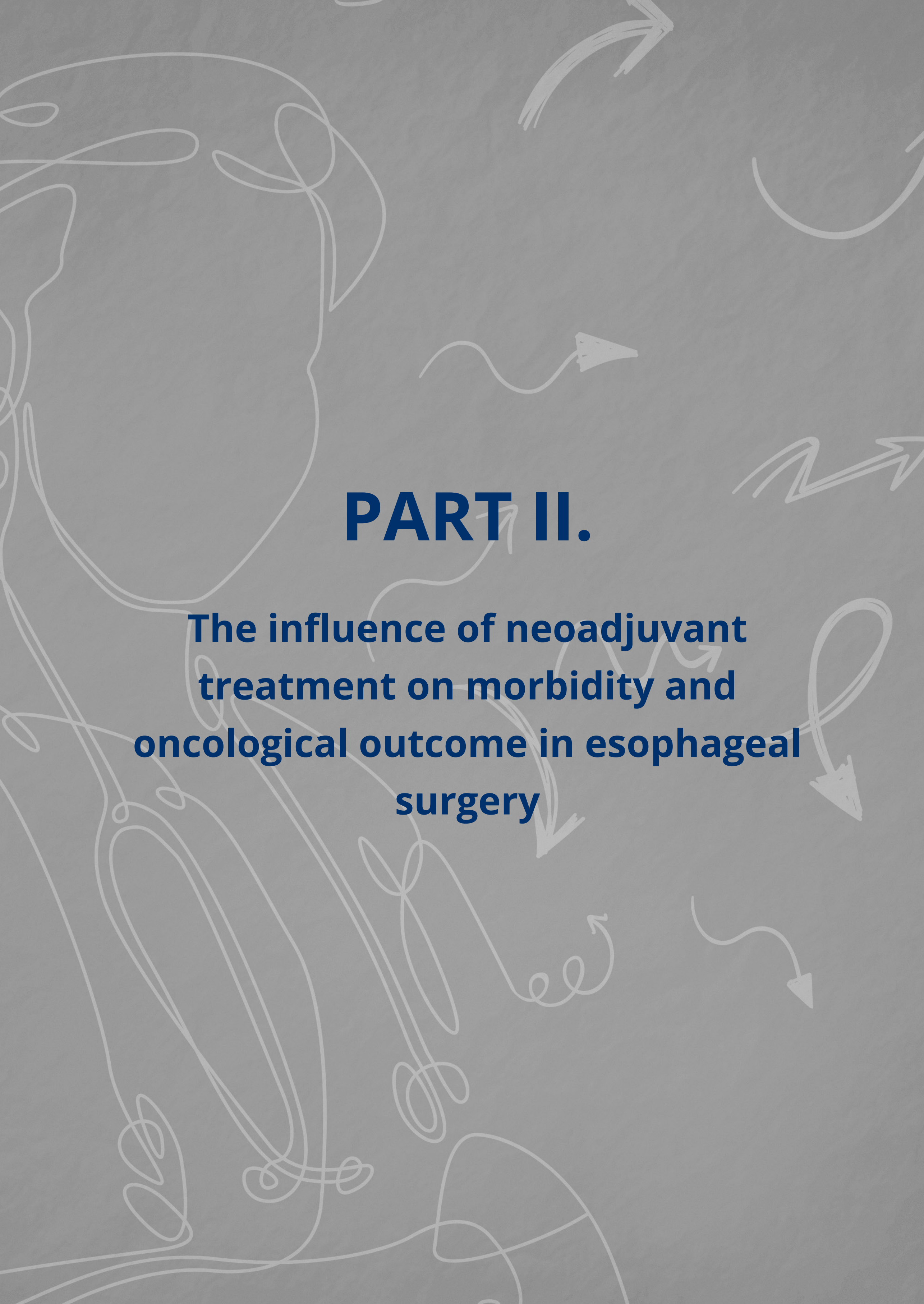


PART II.

The influence of neoadjuvant treatment on morbidity and oncological outcome in esophageal surgery

CHAPTER 6

Perioperative treatment, not surgical approach, influences overall survival in patients with gastro-esophageal junction tumors: A nationwide, population-based study in the Netherlands

Authors:

M. Koëter, MD[1]; K. Parry, MD[2]; R.H.A. Verhoeven, PhD[3]; M.D.P. Luyer, MD, PhD[1]; J.P. Ruurda, MD, PhD[2]; R. van Hillegersberg, MD, PhD[2]; V.E.P.P. Lemmens, PhD[3,4]; G.A.P. Nieuwenhuijzen, MD, PhD[1]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands

[2] Department of Surgery,
University Medical Centre Utrecht, The Netherlands

[3] Comprehensive Cancer Centre,
Eindhoven, The Netherlands

[4] Department of Public Health,
Erasmus University Medical Centre Rotterdam, The Netherlands

Abstract

Background: Resectable gastro-esophageal junction (GEJ) tumors are treated either with an esophageal-cardia resection or with gastrectomy. The difference in outcome between these two treatment modalities is unknown. Therefore, the aim of this study was to evaluate population-based treatment strategies for patients with resectable adenocarcinomas of the GEJ and to compare the oncological outcomes.

Methods: Patients with potentially resectable GEJ tumors diagnosed between 2005 and 2012 were selected from the nationwide, population-based Netherlands Cancer Registry. Differences between patients were compared using the chi-square test. Survival curves were generated using the Kaplan-Meier method. Overall multivariate survival was assessed with Cox regression analyses.

Results: Patients treated with esophagectomy (n=939) were significantly younger than patients treated with gastrectomy (n=257, 64 vs. 66 years, p<0.001). No differences were noted regarding lymph node yield, lymph node ratio and radicality. Patients treated with an esophagectomy or gastrectomy exhibited comparable overall 5-year survival rates (36% vs. 33%, respectively, p=0.250). Multivariate analysis showed that patients receiving perioperative treatment and gastrectomy exhibited similar overall survival rates compared to patients receiving perioperative treatment and esophagectomy (hazards ratio [HR]: 1.0, 95% confidence interval [CI] 0.7-1.3, p=0.923). However, patients receiving esophagectomy alone (HR: 1.4, 95% CI 1.1-1.6, p=0.002) or gastrectomy alone (HR: 1.8, 95% CI 1.4-2.4, p<0.001) exhibited a significantly worse overall survival.

Conclusions: The chosen type of surgery (esophagectomy or gastrectomy) did not influence the overall survival in our cohort of patients with GEJ tumors. The administration of perioperative chemo (radio) therapy improved survival regardless of the surgical approach.

Introduction

The incidence of esophageal cancer has increased over the past two decades, particularly in developed countries, making it the eighth most common cancer worldwide[1-3]. In the Western world, this increased incidence is attributed to an increased incidence of adenocarcinomas, especially of the gastro-esophageal junction (GEJ) in white males[4]. According to the Siewert classification, an adenocarcinoma of the gastro-esophageal junction is a tumor which has its epicentre within 5 cm of the anatomic GEJ[5]. The anatomic GEJ is defined as the proximal end of the gastric folds. According to the 7th edition of the TNM staging system[6], a tumor with the epicentre within 5 cm of the GEJ that extends into the esophagus is classified and staged as an esophageal carcinoma, whereas a tumor with an epicentre within 5 cm of the GEJ without extension in the esophagus is classified and staged as a gastric carcinoma.

Patients with resectable GEJ tumors are either treated via an esophageal resection followed by a reconstruction with a gastric pull-up or by a gastrectomy followed by Roux-en-Y reconstruction. The difference in outcome between these two treatment modalities is unknown. To date, the literature does not provide conclusive evidence regarding the optimal treatment strategy in patients with GEJ tumors[7]. No randomized study has evaluated the optimal treatment strategy for GEJ tumors. This type of study appears to be difficult due to clinical tumor characteristics, such as the extension in the esophagus, that influence the decision whether to perform an esophagectomy or a gastrectomy.

Therefore, the aim of this study was to evaluate population-based patterns of care in treatment strategies for patients with resectable adenocarcinomas of the GEJ and to compare oncological outcomes.

Patients and Methods

Data

Nationwide population-based data from the Netherlands Cancer Registry (NCR) were used. The NCR collects data on all patients with newly diagnosed cancer in all Dutch hospitals. Patient, treatment and tumor characteristics are routinely extracted from the medical records by specially trained registrars of the cancer registry within 9 months after diagnosis. The topography and morphology of the tumors were coded according to the International Classification of Diseases for Oncology (ICD-O-3)[8]. All patients diagnosed with a cancer of the GEJ (C16.0) between 2005 and 2012 were extracted from the NCR. The registry does not provide the Siewert classification, however we defined a GEJ tumor as a tumor with its epicentre within 5cm of the GEJ. For this study, only adenocarcinomas (M8140–M8384) were selected for analysis. Patients diagnosed from 2005 to 2009 were staged according to TNM-6, whereas patients diagnosed from 2010-2012 were staged according to TNM-7[9;10]. Tumor stage recorded by the NCR was defined by histopathological examination of the resected specimen. Clinical tumor stage was primarily determined by computed tomography (CT) scanning and endoscopic ultrasound (EUS) if available. Survival status was obtained from the nationwide population registries network, a nationwide population-based registry that collects information on all deceased Dutch citizens. Institutional Review Board approval was obtained from the NCR.

Patients

Between January 2005 and December 2012, 4050 patients were diagnosed with an adenocarcinoma of the GEJ in the Netherlands. Patients with metastatic disease (n=1620) or unknown/missing M-status (n=307) were excluded. Furthermore, 149 patients with tumors infiltrating surrounding organs (T4) were excluded given that it was uncertain whether these patients were eligible for curative resection. Finally, patients with unknown treatment (n=7) or unknown type of surgical treatment (n=10) were also excluded. This resulted in 1957 patients with a resectable and potentially curable adenocarcinoma of the GEJ (T1-3, N0-3, M0). Of these patients, 1196 (61.1%) received surgical treatment, and these patients were analysed in this study to compare the different types of neoadjuvant and surgical treatment.

Statistical analysis

Differences in patient and tumor characteristics were compared using the Pearson's Chi-square test for nominal data. For differences in continuous variables, the Mann-Whitney U test or the independent T-test were used. Survival curves were obtained using the Kaplan-Meier method, and differences between groups were assessed via the log-rank test. To evaluate independent prognostic factors for survival, uni- and multivariate analyses and Cox regression analyses were performed. All analyses were performed using Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). All reported p-values less than 0.05 were considered statistically significant.

Results

Patients

A total of 1196 patients with resectable and potentially curable adenocarcinoma of the GEJ treated with a surgical resection were evaluated. Mean age was 64.4 years (SD 10.4) (Table 1). The majority of the patients were male (80%). Most patients were clinically diagnosed with a T3 tumor (n=520, 43%) and N+ disease (n=624, 52%). Neoadjuvant therapy was administered in 651 patients (54%) prior to surgery, including perioperative chemotherapy in 385 patients (32%) and neoadjuvant chemoradiation in 266 patients (22%). Esophagectomy was performed in 939 patients (79%), and gastrectomy in the remaining 257 patients (21%).

Esophagectomy vs. gastrectomy

Patients who underwent an esophagectomy were significantly younger than patients treated with gastrectomy (64 vs. 66 years, respectively, $p<0.001$, Table 1). Furthermore, patients treated with esophagectomy exhibited higher clinical T-stages (T3: 45.9% vs. T3: 34.6%) with more clinically positive lymph nodes (55.6% vs. 39.7%) compared with patients treated with gastrectomy. Perioperative chemotherapy was administered in 30% of the patients treated with esophagectomy compared with 40% of the patients treated with gastrectomy ($p=0.002$). More patients treated with esophagectomy were treated with neoadjuvant chemoradiation compared with gastrectomy (25% vs. 11%, respectively) ($p<0.001$). No significant differences were observed with respect to lymph node yield, total number of positive lymph nodes, lymph node ratio and the radicality of the resection between the two types of surgical approaches (Table 2).

Table 1. Baseline patient characteristics for patients treated with esophagectomy or gastrectomy.

	All patients (n=1196)	Esophagectomy (n=939, 78.5%)	Gastrectomy (n=257, 21.5%)	p-value
Mean age (years, SD)	64.4 (SD 10.4)	63.9 (SD 10.1)	66.4 (SD 11.4)	<0.001
Gender				
Male	954 (79.8%)	761 (81.0%)	193 (75.1%)	
Female	242 (20.2%)	178 (19.0%)	64 (24.9%)	0.036
cT stage				
T1	33 (2.8%)	23 (2.4%)	10 (3.9%)	
T2	308 (25.8%)	254 (27.1%)	54 (21.0%)	
T3	520 (43.5%)	431 (45.9%)	89 (34.6%)	
Tx (unknown/missing)	335 (28.0%)	231 (24.6%)	104 (40.5%)	<0.001
cN-stage				
N0	445 (37.2%)	325 (34.6%)	120 (46.7%)	
N+	624 (52.2%)	522(55.6%)	102 (39.7%)	
Nx (unknown/missing)	127 (10.6%)	92 (9.8%)	35 (13.6%)	<0.001
Perioperative therapy				
None	545 (45.6%)	419 (44.6%)	126 (49.0%)	
Chemotherapy	385 (32.2%)	282 (30.0%)	103 (40.1%)	
Chemoradiation	266 (22.2%)	238 (25.3%)	28 (10.9%)	<0.001

Table 2. Histopathological characteristics.

	Esophagectomy (n=939, 78.5%)	Gastrectomy (n=257, 21.5%)	p-value
Tumor differentiation			
Well	26 (2.8%)	12 (4.7%)	
Moderate	223 (23.7%)	59 (23.0%)	
Poor	403 (42.9%)	117(45.5%)	
Unknown	287 (30.6%)	69 (26.8%)	0.308
Tumor stage[a]			
I	198 (21.5%)	68 (27.5%)	
II	246 (26.7%)	63 (25.5%)	
III	447 (48.6%)	103 (41.7%)	
IV	29 (3.2%)	13(5.3%)	0.056
Lymph node yield (SD)[b]	16.0 (SD 9.1)	15.8 (SD 9.3)	0.813
Positive lymph nodes (SD)[c]	3.31 (SD 4.6)	3.23 (SD 5.6)	0.132
Lymph node ratio	0.37	0.37	0.951
R-status[d]			
R0	786 (86.7%)	209 (83.6%)	
R1/2	121 (13.3%)	41 (16.4%)	0.217

[a] Exclusion of unknown (n=29)

[b] Exclusion of unknown (n=23)

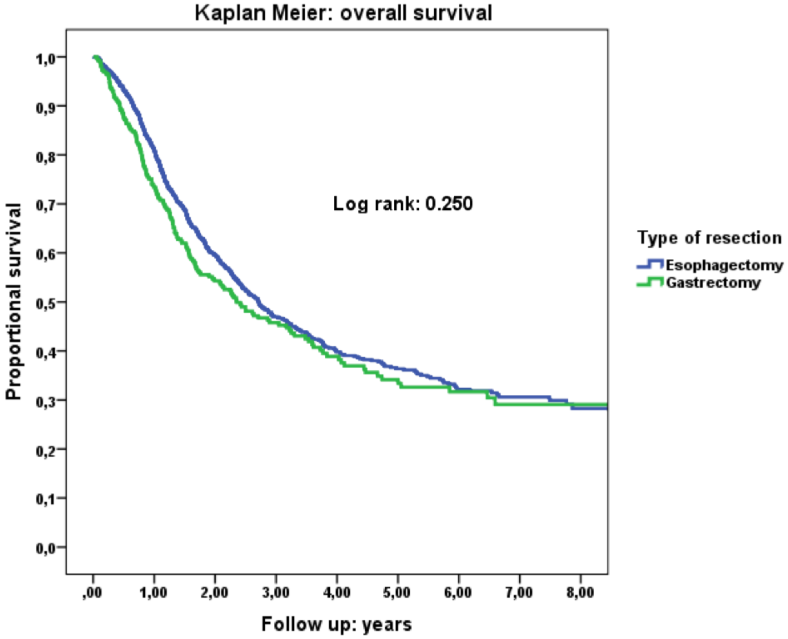
[c] Exclusion of unknown (n=19)

[d] Exclusion of unknown (n=39)

Survival

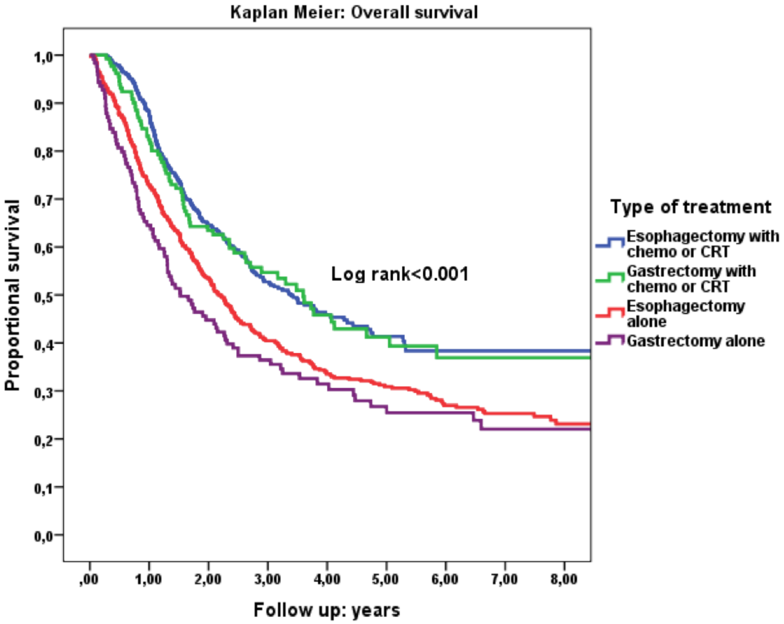
Patients treated with an esophagectomy or gastrectomy exhibited comparable overall 5-year survival rates (36% vs. 33%, respectively, p=0.250, Figure 1). Additionally, no significant difference was observed between esophagectomy and gastrectomy in patients who were treated with perioperative therapy (41% vs. 41%, respectively, p=0.787). However, the overall 5-year survival in the group receiving surgery combined with perioperative therapy was significantly higher compared with esophagectomy alone (31%) or gastrectomy alone (26%, p<0.001), (Figure 2). No significant difference in 5-year overall survival was noted in patients treated with chemotherapy or chemoradiation (43% vs. 39%, p=0.323).

Figure 1. Overall survival of patients with a resectable adenocarcinoma of the GEJ treated with an esophagectomy or gastrectomy.



Numbers at risk	0	1	2	3	4	5	6	7	8
Esophagectomy	939	760	477	312	209	149	97	59	30
Gastrectomy	257	188	130	90	60	45	32	17	9

Figure 2. Overall survival of patients with a resectable adenocarcinoma of the GEJ treated with surgery alone or surgery with chemotherapy or chemoradiation (CRT)



Numbers at risk	0	1	2	3	4	5	6	7	8
Esophagectomy with chemo or CRT	520	456	264	156	88	51	25	8	3
Gastrectomy with chemo or CRT	131	107	75	49	32	23	13	4	2
Esophagectomy	416	303	212	155	121	98	72	51	27
Gastrectomy	124	80	54	40	27	21	17	12	7

Multivariate analyses showed that patients greater than 70 years of age, male gender, high tumor stage and R1-resection were significantly associated with a worse overall survival. Good tumor differentiation and tumor stages I and II were significantly associated with a better overall survival. Regarding the treatment strategy, patients receiving perioperative treatment and gastrectomy exhibited similar overall survival compared with patients receiving perioperative treatment and esophagectomy (hazard ratio [HR]: 1.0, 95% confidence interval [CI] 0.8-1.3, p=0.923). However, patients receiving an esophagectomy (HR: 1.4, 95% CI 1.1-1.6, p=0.002) or gastrectomy alone (HR: 1.8, 95% CI 1.4-2.4, p<0.001) exhibited a significantly worse overall survival (Table 3).

Table 3. Multivariable Cox regression analysis on overall survival.

		Univariable			Multivariable		
	Number of patients (n=1196)	HR	95% CI	p-value	HR	95% CI	p-value
Age							
<70	781	1.0			1.0		
≥70	415	1.4	1.2-1.6	<0.001	1.4	1.2-1.6	<0.001
Gender							
Male	954	1.0			1.0		
Female	242	0.8	0.7-1.0	0.051	0.7	0.6-0.9	0.001
Treatment							
Esophagectomy with chemo or CRT	520	1.0			1.0		
Gastrectomy with chemo or CRT	131	1.0	0.8-1.4	0.756	1.0	0.8-1.3	0.923
Esophagectomy alone	416	1.5	1.3-1.8	<0.001	1.4	1.1-1.6	0.002
Gastrectomy alone	124	1.8	1.4-2.2	<0.001	1.8	1.4-2.4	<0.001
Other	5	1.5	0.5-4.5	0.522	1.8	0.6-5.8	0.327
Tumor differentiation							
Good	38	0.5	0.3-0.9	0.011	0.6	0.4-1.0	0.042
Moderate	282	0.8	0.6-0.9	0.004	0.9	0.7-1.0	0.108
Poor	519	1.0			1.0		
Unknown	356	0.6	0.5-0.7	<0.001	0.7	0.6-0.9	0.002
Tumor stage (pathologic)							
I	266	0.3	0.3-0.4	<0.001	0.3	0.3-0.4	<0.001
II	309	0.7	0.6-0.8	<0.001	0.7	0.6-0.8	<0.001
III	550	1.0			1.0		
IV	42	2.2	1.5-3.0	<0.001	2.0	1.4-2.9	<0.001
Unknown	29	0.3	0.2-0.6	<0.001	0.4	0.2-0.8	0.013
Radicality							
R0	995	1.0			1.0		
R1/2	162	2.5	2.1-3.0	<0.001	1.8	1.5-2.2	<0.001
Unknown	39	1.8	1.2-2.6	0.002	1.5	1.0-2.2	0.031

Discussion

This large nationwide, population-based study showed that patients with a resectable GEJ tumor in the Netherlands and were treated with surgery received an esophagectomy in 79% and gastrectomy 21% of the cases. Similar surgical outcomes were noted between the two types of resection with respect to lymph node yield, lymph node ratio and radicality. No survival difference was observed between patients treated with esophagectomy or gastrectomy regardless of neoadjuvant treatment. However, perioperative chemotherapy and neoadjuvant chemoradiation were most crucial for oncological outcome.

Tumor location is important in choosing the most optimal surgical approach. In particular, extension of the tumor in the esophagus influences the decision whether to perform an esophagectomy or gastrectomy. Previous studies have reported difficulties in determining the exact localization and extent of the tumor. Additionally, in the evaluation of the nodal status, a discrepancy between preoperative findings and postoperative histopathological outcome is observed[11]. These findings may impede decision making related to the treatment approach. This study showed that the majority of patients with GEJ tumors in the Netherlands are treated according to the guidelines for esophageal cancer. The definition of GEJ tumors was based on the clinical definition as recorded in medical files, which may vary between hospitals, but reflects everyday clinical practise. Therefore, it is difficult to differentiate which tumor-related factors were used to determine whether the tumor was treated via esophagectomy or gastrectomy.

In this study, no survival difference was noted between patients treated with esophagectomy or gastrectomy regardless of the use of neoadjuvant treatment. However, the baseline characteristics in clinical tumor stage between the esophagectomy and gastrectomy group differed with a higher cT-stage and more cN+ disease observed in patients receiving an esophagectomy. Although we corrected for tumor staging in our multivariable survival analysis, the high number of unknown T and N stages potentially influenced the results.

This study revealed no differences between esophagectomy and gastrectomy regarding lymph node yield, lymph node ratio and radicality of the resection. These findings are consistent with previous studies and demonstrate no benefit for an esophagectomy or gastrectomy for these parameters[12-14]. A radical resection (R0) in the current study was performed in 84% of patients treated with esophagectomy and in 81% treated with gastrectomy. In the literature, R0 resection rates ranges from 72 to 93% for esophagectomy and from 62 to 93% for gastrectomy[7]. Several studies demonstrated that a wide proximal resection margin (>3.8 to 6 cm) was associated with an improved survival[12;13]. Theoretically, this margin width is difficult to achieve with a gastrectomy and more easily obtained with an esophagectomy. Also, it would be expected that an esophagectomy would result in more extensive lymph node dissection because it includes an additional mediastinal lymphadenectomy. However, in this study, a significant difference in the lymph node yield, the number of positive lymph nodes or the lymph node ratio was not established. Additionally, with regard to overall survival, we did not observe a difference between the two surgical strategies as previously reported in the literature[13;15-18]. This observation was independent of perioperative treatment. A recent study showed an unadjusted survival benefit for patients receiving an esophagectomy. However, this benefit disappeared after adjusted survival analysis[19]. These findings indicate that the type of surgery chosen based on clinical factors in GEJ cancer does not influence oncological outcomes. A possible explanation could be the fact that the sites with the most affected lymph nodes in GEJ tumors are paracardial and near the lesser curvature[17;18;20]. A full lymphadenectomy of these stations is generally being performed in both esophagectomy and gastrectomy. Nevertheless, a full lymphadenectomy of upper mediastinal nodes (of which involvement is present in 11% of type II GEJ tumors[17]) can only be achieved via a transthoracic esophagectomy. In our study, patients with clinically positive lymph nodes received an esophagectomy more often, indicating that an esophagectomy is more often chosen when mediastinal lymph node positivity was expected. Furthermore, this might have influenced pathologic staging since it might lead to stage migration. This study showed more stage III tumors in the esophagectomy group, however this difference was not significant. Nevertheless, a recent study demonstrated that the number of resected nodes was not associated with survival after neoadjuvant chemoradiation, which questions the importance of the extent of the lymphadenectomy in case of neoadjuvant chemoradiation followed by an esophagectomy[21].

Neoadjuvant chemoradiation and perioperative chemotherapy are beneficial in the treatment of both esophageal and GEJ tumors, respectively, based on the CROSS-trial[22] and the MAGIC-trial[23]. Based upon multivariate analysis in this study, perioperative treatment of GEJ tumors via chemotherapy or chemoradiation prior to surgery significantly improved overall survival, whereas the type of surgery did not. This result is consistent with a recent study of the NSQIP/SEER data. In these data, the type of resection did not significantly influence survival compared with multimodality treatment, which improved survival[19]. However, data on chemotherapy were lacking, and radiation was used as a surrogate for multimodality treatment. There is no conclusive evidence in the literature on which perioperative treatment (chemotherapy or chemoradiation) regime should be used in the treatment of GEJ tumors. The CROSS trial[22] and the MAGIC trial[23] both included GEJ tumors. A meta-analysis[24] revealed a survival benefit of neoadjuvant chemoradiotherapy or chemotherapy compared with surgery alone in both esophageal and GEJ carcinoma patients. In our study, no difference in 5-year survival was noted between perioperative chemotherapy and chemoradiation. A clear advantage for chemotherapy or chemoradiation in GEJ tumors has not been established in the literature to date. An early, closed phase III trial by Stahl et al.[25] revealed a non-significant survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the esophago-gastric junction. A randomised phase II trial by Burmeister et al.[26] revealed no survival difference; however, chemoradiotherapy resulted in a significantly increased pathological response and R0 resection rate and thus appeared to advantageous for bulky GEJ tumors. An Irish trial is currently recruiting patients with esophageal and GEJ tumors to compare the MAGIC regimen with the CROSS regimen. This study might provide more insight into the optimal preoperative strategy.

Given that oncological findings appear to be similar, patient-related outcomes with respect to morbidity, mortality, hospital stay and quality of life are even more important in decision making regarding the optimal surgical treatment strategy. Unfortunately, we did not have insight into these factors. A recent study reported adjusted 30-day mortality rates for esophagectomy and gastrectomy in the Netherlands of 4.6% and 6.9%, respectively[27]. Several additional studies addressed mortality and morbidity rates and found no difference in mortality between esophagectomy and gastrectomy[13;16;17]. According to the literature, the morbidity rates of both surgical strategies appear to be comparable, with a morbidity rate ranging from 33 to 77% after esophagectomy and from 11 to 67% after gastrectomy[15-17]. Only one of these studies revealed increased morbidity after esophagectomy. Two studies demonstrated that quality of life after surgery was more severely affected by esophagectomy compared with gastrectomy[28;29]; however, these studies involved a relatively small study population.

Our study has strengths and limitations. The definition of GEJ tumors was based on various clinical definitions as recorded in the medical files, and these definitions may vary between hospitals. We excluded all T4 tumors given that it was impossible to identify T4 tumors that were potentially eligible for surgery with or without neoadjuvant treatment. Given that a CT scan but not always a EUS was performed in each patient, we observed a relatively large number of unknown or missing T stages (n=355), and this limitation potentially influenced our results. Another limitation of this study was that the NCR does not provide data on whether or not the patients received the whole course of perioperative chemotherapy or neoadjuvant chemoradiation. According to the Dutch guidelines patients treated with an esophageal scheme were advised to receive neoadjuvant chemoradiation followed by esophagectomy and patients treated with a gastric scheme should receive perioperative chemotherapy. Unfortunately, in the NCR database it is not registered whether or not the patients received the whole course of perioperative treatment (CRT or chemotherapy). Despite the fact that some patients may not fully completed the perioperative treatment, this study still revealed an important influence of perioperative treatment. Therefore the observed phenomenon might even underestimate the effect of a ideally fully completed perioperative scheme. In this study only 54% of the patients received perioperative chemotherapy or neoadjuvant chemoradiation, this is probably due to the fact that our study has started in 2005 and the randomized trials like the Magic and CROSS trials were still ongoing. As a consequence, the use of perioperative chemotherapy or neoadjuvant chemoradiation increased from 31% in the period 2005-2008 to 78% in the period 2009-2012. The strengths of this study are its large number of patients and its observational nature with no patient selection; therefore, it represents the entire population and provides an overview of everyday clinical practise.

In conclusion, this nationwide cohort study revealed no difference in surgical outcomes in patients with a resectable GEJ tumor treated with esophagectomy or gastrectomy with respect to lymph node yield, lymph node ratio, radicality and overall survival. Perioperative treatment with chemotherapy or chemoradiation rather than the surgical approach appears to be most critical for overall survival.

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CHAPTER 7

Delaying surgery after neoadjuvant chemoradiotherapy does not significantly influence postoperative morbidity or oncological outcome in patients with esophageal adenocarcinoma

Authors:

N. Kathiravetpillai, MD[1]; M. Koëter, MD[1]; M.J.C. van der Sangen, MD, PhD[2];
GJ Creemers, MD, PhD[3]; M.D.P. Luyer, MD, PhD[1]; H.J.T. Rutten MD, PhD[1];
G.A.P. Nieuwenhuijzen, MD, PhD[1]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands

[2] Department of Radiation Oncology,
Catharina Hospital Eindhoven, The Netherlands

[3] Department of Oncology,
Catharina Hospital Eindhoven, The Netherlands

Abstract

Background: Patients with resectable esophageal cancer are treated with neoadjuvant chemoradiotherapy (nCRT) followed by surgery within 3 to 8 weeks. In practice, surgery is often delayed for various reasons. The aim of this study was to evaluate whether delaying surgery beyond 8 weeks has an effect on postoperative morbidity, long-term survival, and pathologic response in patients treated for esophageal ADC.

Methods: Patients who underwent nCRT followed by surgery, for cT1-3, N0-3, M0 ADC between 2001 and 2014 were retrospectively included from a prospectively obtained database. Patients with a time from the end of nCRT to surgery (TTS) ≤ 8 weeks were compared with patients with a TTS > 8 weeks.

Results: Of 190 patients, 65 had a TTS ≤ 8 weeks, and 125 had a TTS > 8 weeks. Patient characteristics were comparable for both groups, but patients with TTS > 8 weeks exhibited higher ASA scores (p = 0.013) and more comorbidities (p = 0.007). Multivariate analysis revealed that TTS did not significantly influence postoperative morbidity, pathologic complete response rates, and five-year survival rates (42% in patients with TTS ≤ 8 weeks and 37% in patients with TTS > 8 weeks).

Conclusions: Delaying surgery beyond 8 weeks after nCRT did not significantly influence postoperative morbidity, pathologic response, and survival in patients with non-metastatic ADC. Therefore, it appears reasonable to postpone surgery beyond 8 weeks in patients who have not yet recovered from nCRT. However, if the patient is fit for surgery, postponing surgery does not have any additional advantages.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by radical surgery improves overall survival and locoregional control in patients with non-metastatic locally advanced esophageal cancer[1-3]. Postoperative morbidity rates after esophagectomy vary between 26% and 66.7%[4-6]. Several factors influence postoperative morbidity rates, such as patient characteristics (age, smoking, and the presence of comorbidities) and surgical approach. Postoperative morbidity is also influenced by nCRT[7;8]. According to clinical guidelines, surgery is performed 3 to 8 weeks after completion of nCRT; this guideline is typically followed in randomised controlled trials[9-11]. This period allows acute inflammation to resolve following nCRT, patients to recuperate from neo-adjuvant treatment, and patients to be fit for surgery. In practice, however, surgery is often postponed beyond this timeframe due to the toxicity of nCRT and the patient condition. Time to surgery (TTS) may further depend on logistical reasons[12-14] and the patient's personal preference.

Delaying surgery may affect postoperative outcome given that nCRT is associated with inflammation and fibrosis in the surgical field[15]. Furthermore, radiation-induced fibrosis or radionecrosis could complicate surgery and postoperative recovery[16]. Finally, postponing surgery after nCRT may influence oncological outcome. On the one hand, a longer wait time could result in more tumor regression; however, this waiting period may lead to the progression of (systemic) disease[15;17;18]. In rectal cancer, postponing surgery beyond 8 weeks is associated with higher rates of pathologic complete response (pCR)[19-21]. Additionally, postoperative morbidity, mortality, and overall survival were not significantly influenced by the interval between nCRT and surgery[19-22].

Several studies suggest that patients with esophageal squamous cell carcinoma (SCC) benefit more from nCRT than patients with adenocarcinoma (ADC). In the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) trial, patients with SCC exhibited an increased pCR rate and better survival compared with patients with ADC[3]. Given its lower response rate, increasing TTS in ADC patients may have less of an influence on tumor regression compared with SCC patients. Little is known about the optimal timing of surgery after nCRT in ADC. Retrospective studies have shown conflicting results about whether or not delaying surgery is beneficial with respect to pathological response[17;18;23-27]. These studies, however, mainly focused on SSC of the esophagus, whereas most tumors in the Western population currently are ADC. Kim et al.[18] performed a retrospective study in ADC patients, in which delaying surgery did not affect pathologic response. However, a recent study in SCC and ADC patients by Shapiro et al.[25] indicated that increasing TTS improved pathologic response with a trend towards more postoperative complications. Others however showed that delaying surgery beyond 8 weeks was not associated with more postoperative complications[17;18;24-26].

The aim of this study was to evaluate the influence of the time period between nCRT and surgery on the postoperative course, pathological response, and long-term survival in patients with ADC.

Methods

A database of all patients with esophageal cancer treated at the Catharina Hospital in Eindhoven in the Netherlands was obtained and retrospectively analysed for patients treated between 1 January, 2001 and 1 May, 2014. All data concerning diagnosis, treatment, and follow-up were recorded. In all patients, the standard work-up included a clinical examination, endoscopy with biopsies, endoscopic ultrasonography (EUS), ultrasonography or computer tomography (CT) of the cervical region, CT of the chest and abdomen, and a whole body positron emission tomography fused with CT (PET-CT. Follow-up data were updated every 6 months based on outpatient-clinic reports.

Patients were recruited into this study if they were diagnosed with cT1-3, N0-3, M0 (TNM 7th edition) ADC and underwent nCRT followed by an esophagectomy. Neoadjuvant therapy consisted of 23 fractions of 180 cGy three-dimensional (3D) conformal radiotherapy, which was administered 5 days a week, combined with 5 weekly intravenous administrations of paclitaxel (50 mg/m^2) and carboplatin (AUC 2). Because of inclusion in a phase II trial[28], patients treated between 2001 and 2004 were treated with a different regimen which consisted of paclitaxel 175mg/m^2 intravenously and carboplatin AUC 5 intravenously on day 1 and day 22 and continuous infusion of 5-FU 200mg/m^2 on day 1 through day 42. The surgical approach was changed in this period from an open transhiatal or transthoracic approach to a laparoscopic transhiatal, and recently, to a completely, minimally invasive thoracolaparoscopic approach. The exclusion criteria were SCC and a tumor located in the proximal esophagus. Furthermore, we excluded patients who underwent salvage surgery, which was defined as an esophagectomy for tumor recurrence after initial chemoradiotherapy (dCRT).

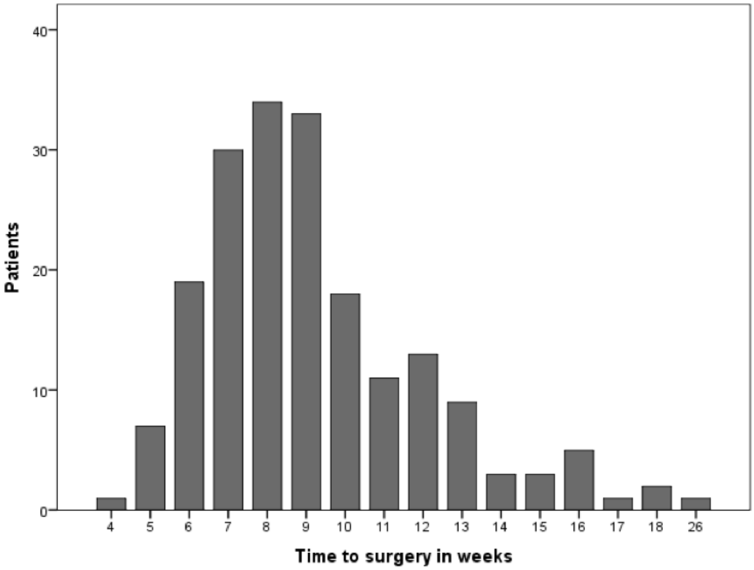
Patients were divided into two groups based on the time to surgery (TTS) after completion of neoadjuvant chemoradiotherapy. One group consisted of patients with a TTS ≤ 8 weeks; the other group with a TTS > 8 weeks. We compared both groups for perioperative course, postoperative mortality, long-term survival, pCR (ypT0N0), and Mandard tumor regression grade to evaluate the response of the tumor to nCRT[29]. Postoperative mortality was defined as death within 30 days or during the hospital stay.

Univariable analysis was performed by means of χ^2. Survival was defined as the time between surgery and death or the date of last follow-up. In March 2015, the survival status of the patients was recorded. Survival analysis was performed using the Kaplan-Meier method, and comparisons were analysed using the log-rank test. For multivariable analysis, we used binary logistic regression and Cox' regression analysis to determine independent predictors for perioperative complications and survival. TTS (≤ 8 weeks and > 8 weeks) was used as a dichotomous variable for perioperative course and survival. For analysis of pathologic response, TTS was considered as a continuous variable. The following variables were also included in multivariable analysis: age, sex, number of comorbidities, American Society of Anesthesiologists classification, need for tube feeding, weight loss, tumor location, and surgical approach. Analyses were performed using Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered significant.

Results

In a period between 1 January, 2001 and 1 May, 2014, 387 patients were treated for resectable esophageal carcinoma at our center of which 190 patients met the inclusion criteria and were further analysed. Sixty-five patients had a TTS ≤ 8 weeks, and 125 patients had a TTS > 8 weeks. The distribution of the time intervals between the completion of nCRT and esophagectomy is presented in Figure 1. The median duration of the interval between completion of nCRT and surgery within the patients with a TTS ≤ 8 weeks was 50 days and 70 days for patients with a TTS > 8 weeks. The groups did not significantly differ in age, sex, clinical T-stadium, tumor location, weight loss at diagnosis, and need for enteral tube feeding after nCRT. Patients with a TTS > 8 weeks exhibited significantly more co-morbidities and a higher ASA classification (Table 1).

Figure 1. Distribution of the timing (in weeks) of esophagectomy after completion of nCRT.



A transthoracic approach was performed in 30.8% of patients with a TTS ≤ 8 weeks and in 43.2% of patients with a TTS > 8 weeks (p = 0.096). A R0 resection was performed in 61 patients (93.8%) with a TTS ≤ 8 weeks and in 115 patients (92.0%) with a TTS > 8 weeks. Operative outcomes, such as duration of surgery, blood loss, and need for intra-operative blood transfusion, were comparable between both groups (Table 2). The mean duration of surgery did not differ between patients with a TTS ≤ 8 weeks and patients with a TTS > 8 weeks. The median hospital stay was similar between both groups: 11 (range 7 to 82) days in patients with a TTS ≤ 8 weeks and 12 (range 6 to 89) days in patients with TTS > 8 weeks (p = 0.459). Five patients with a TTS ≤ 8 weeks and 19 patients with a TTS > 8 weeks were readmitted within 30 days after discharge from the hospital (p = 0.139). A total of 33 patients were readmitted to the ICU, of which 26 patients had a TTS > 8 weeks (p = 0.083).

Table 1. Demographic and tumor characteristics depending on the time to surgery after completion of nCRT

	TTS ≤ 8 weeks N = 65 (%)	TTS > 8 weeks N = 125 (%)	Overall N = 190 (%)	p- Value
Sex				
Female	11 (16.9)	10 (8.0)	21 (11.1)	
Male	54 (83.1)	115 (92.0)	169 (88.9)	0.063
Age				
≤ 65 year	42 (64.6)	66 (52.8)	108 (56.8)	
> 65 year	23 (35.4)	59 (47.2)	82 (43.2)	0.119
Comorbidity				
0	24 (36.9)	26 (20.8)	50 (26.3)	
1	25 (38.5)	41 (32.8)	66 (34.7)	
≥ 2	16 (24.6)	58 (46.4)	74 (38.9)	0.007
ASA score				
I	18 (28.1)	18 (14.5)	36 (19.1)	
II	43 (67.2)	86 (69.4)	129 (68.6)	
III	3 (4.7)	20 (16.1)	23 (12.2)	0.013
Tumor location				
Mid- thoracic esophagus	2 (3.1)	6 (4.9)	8 (4.3)	
Distal thoracic esophagus	48 (73.8)	83 (68.0)	131 (70.1)	
GE-junction	15 (23.1)	33 (27.0)	48 (25.7)	0.670
cT stage				
cT1	1 (2.0)	0 (0.0)	1 (0.6)	
cT2	2 (4.0)	10 (9.0)	12 (7.5)	
cT3	47 (94.0)	101 (91.0)	148 (91.9)	0.181
cN stage				
cN0	14 (29.8)	30 (27.0)	44 (27.8)	
cN1	28 (59.6)	53 (47.7)	81 (51.3)	
cN2	5 (10.6)	24 (21.6)	29 (18.4)	
cN3	0 (0.0)	2 (1.8)	2 (1.3)	0.374
Weight loss at diagnosis				
0%	25 (39.7)	41 (33.6)	66 (35.7)	
≤ 10%	25 (39.7)	61 (50.0)	86 (46.5)	
> 10%	13 (20.6)	20 (16.4)	33 (17.8)	0.407
Enteral tube feeding during/after nCRT	11 (17.5)	32 (25.8)	43 (23.0)	0.200

Table 2. Surgical data for each group

	TTS ≤ 8 weeks N = 65 (%)	TTS > 8 weeks N = 125 (%)	Overall N = 190 (%)	p-Value
Esophagectomy approach				
Transhiatal approach	45 (69.2)	71 (56.8)	116 (61.1)	
Transthoracic approach	20 (30.8)	54 (43.2)	74 (38.9)	0.096
Level of anastomosis				
Cervical	55 (84.6)	85 (68.0)	140 (73.7)	
Intrathoracic	10 (15.4)	40 (32.0)	50 (26.3)	0.014
Duration of surgery > 4 hours	14 (21.5)	37 (29.6)	51 (26.8)	0.234
Perioperative complications	3 (4.6)	13 (10.4)	16 (8.4)	0.173
Blood transfusion during surgery	2 (3.1)	8 (6.4)	10 (5.3)	0.499

The overall complication rate, regardless of the severity of the complication, was 64.6% in patients with a TTS ≤ 8 weeks and 70.4% of patients with a TTS > 8 weeks ($p = 0.416$). As presented in Table 3, no significant differences were observed in postoperative mortality, anastomotic complications, pulmonary complications, and major complications (Clavien-Dindo score of 3B or greater)[30]. Multivariable analysis revealed that TTS did not significantly influence the occurrence of postoperative complications. Age was the only significant predictor of overall complication rate (odds ratio (OR) 1.056, 95% confidence interval (CI) [1.007-1.106], $p = 0.023$) and, in particular, pulmonary complications (age ≤ 65 years vs. age > 65 years: OR 0.462, 95% CI [0.240-0.891], $p = 0.021$). An independent predictor of anastomotic leakage was tumor location (mid-thoracic esophageal tumor vs. distal tumor OR 12.871, 95% CI [1.402-118.157], $p = 0.024$). The Clavien-Dindo grade 3B or greater complication rate was 16.9% in patients with a TTS ≤ 8 weeks and 29.6% in patients with TTS ≥ 8 weeks ($p = 0.056$) Multivariable analysis revealed that TTS did not influence the occurrence of these major complications. Thirty patients required surgery due to complications (7 relaparotomies, 11 rethoracoscopies, 4 rethoracotomies, and 8 drainages of the cervical wound). Seven patients (10.8%) had a TTS ≤ 8 weeks, and 23 (18.4%) patients had a TTS > 8 weeks ($p = 0.171$). Multivariable analysis revealed that TTS did not significantly influence the occurrence of interventions or reoperations. Compared with the transthoracic approach, the transhiatal approach was a significant predictor of fewer interventions (OR 0.421, 95% CI [0.200-0.890]) and reoperations (OR 0.243, 95% CI [0.104-0.569]).

Fifty patients (26%) exhibited a pCR. The distribution of TTS is presented in Table 4. Logistic regression analysis showed that TTS did not significantly influence the occurrence of pCR. Furthermore, TTS did not significantly influence the magnitude of the response to nCRT since a good response (Mandard score of TRG 1, 2, or 3) was observed in 55.7% of patients with a TTS ≤ 8 weeks and in 46.3% of patients with a TTS > 8 weeks) (OR 1.015, 95% CI [0.999-1.03 1], $p = 0.065$).

The five-year overall survival rate did not significantly differ between the groups TTS ≤ 8 weeks (42%) and TTS > 8 weeks (37%, $p = 0.430$) (Figure 2). Multivariate Cox regression analysis revealed that TTS did not influence survival (HR 0.806, 95% CI [0.508-1.254], $p = 0.339$). Locoregional or distant recurrence occurred in 73 patients; 28 patients (43.1%) had a TTS ≤ 8 weeks, and 45 patients (36.0%) had a TTS > 8 weeks. TTS did not significantly influence recurrence rate (OR 1.345, 95% CI [0.730-2.481]). Median disease-free survival did not significantly differ between the two groups with a median disease-free survival of 4.24 and 4.81 years, respectively ($p = 0.495$) (Figure 3).

Table 3. Postoperative course

	TTS ≤ 8 weeks N = 65 (%)	TTS > 8 weeks N = 125 (%)	Overall N = 190 (%)	p-Value
Complications	42 (64.6)	88 (70.4)	130 (68.4)	0.416
Anastomotic complications *	13 (20.0)	37 (29.6)	50 (26.3)	0.154
Clavien –Dindo score				
< 3B	56 (86.2)	95 (76.0)	151 (79.5)	
≥ 3B	9 (13.8)	30 (24.0)	39 (20.5)	0.100
Pulmonary adverse events	24 (36.9)	61 (48.8)	85 (44.7)	0.118
ARDS	3 (4.6)	6 (4.8)	9 (4.7)	1.000
Pneumonia	16 (24.6)	42 (33.6)	58 (30.5)	0.202
Empyema thoracis	3 (4.6)	12 (9.6)	15 (7.9)	0.227
Interventions	11 (16.9)	37 (29.6)	48 (25.3)	0.056
Endoscopic	2 (3.1)	16 (12.8)	18 (9.5)	0.030
Radiologic	3 (4.6)	4 (3.2)	7 (3.7)	0.692
Reoperation	8 (12.3)	26 (20.8)	34 (17.9)	0.147
Re-admission ≤ 30 days	5 (7.7)	19 (15.2)	24 (12.6)	0.139
Postoperative mortality	3 (4.8)	6 (4.8)	9 (4.8)	1.000

** anastomotic complications are either anastomotic leakage or conduit necrosis.*

Table 4. Pathologic outcome

	TTS ≤ 8 weeks N = 65 (%)	TTS > 8 weeks N = 125 (%)	Overall N = 190 (%)	p-Value
Resection radicality				
R0	61 (93.8)	115 (92.0)	176 (92.6)	
R1	4 (6.2)	10 (8.0)	14 (7.4)	0.775
ypT-stadium				
ypT 0	19 (29.2)	28 (22.4)	47 (24.7)	
ypT 1	9 (13.8)	29 (23.2)	38 (20.0)	
ypT 2	15 (23.1)	23 (18.4)	38 (20.0)	
ypT 3	21 (32.3)	45 (36.0)	66 (34.7)	
ypT 4	1 (1.5)	0 (0)	1 (0.5)	0.250
ypN stadium				
ypN 0	42 (64.6)	74 (59.2)	116 (61.1)	
ypN 1	18 (27.7)	29 (23.3)	47 (24.7)	
ypN 2	5 (7.7)	16 (12.8)	21 (11.1)	
ypN3	0 (0)	6 (4.8)	6 (3.2)	0.215
Pathologic complete response				
pCR	19 (31.1)	31 (25.6)	50 (27.5)	
Non-pCR	42 (68.9)	90 (74.4)	132 (72.5)	0.430
Mandard score				
TRG 1&2	34 (55.7)	50 (46.3)	84 (49.7)	
TRG 3,4&5	27 (44.3)	58 (53.7)	85 (50.3)	0.265

Figure 2. Overall survival

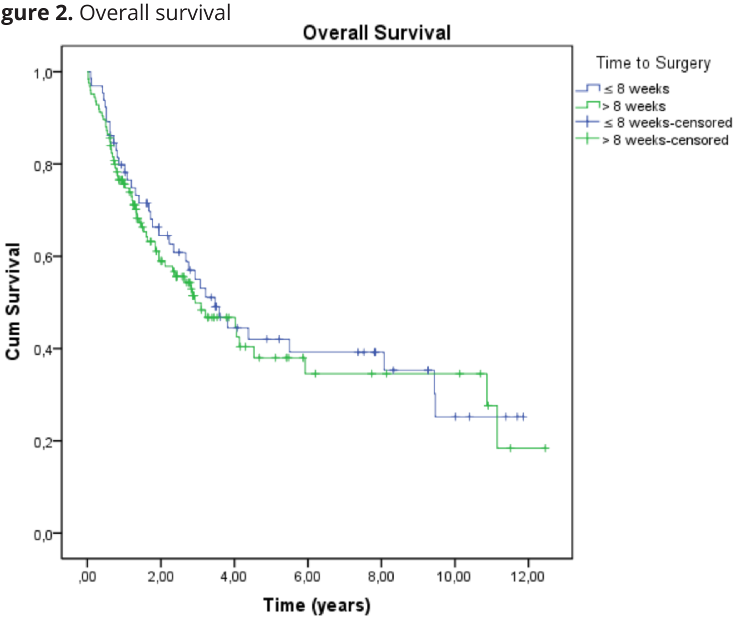
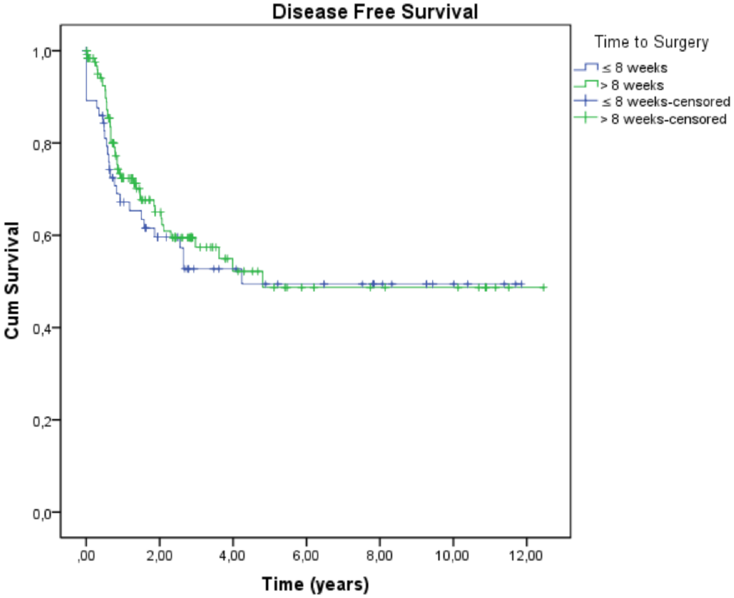


Figure 3. Disease-free survival



Discussion

In this study, we analysed the influence of delaying surgery beyond 8 weeks after completion of nCRT on postoperative morbidity, pathologic response, and overall survival in patients diagnosed with cT1-3, N0-3, M0 ADC of the esophagus. Because ADC is one of the major afflictions in the Western world and given the reduced response rate of ADC to nCRT compared with SCC, we excluded SCC patients and exclusively focused on ADC patients. Overall, our findings suggested that delaying surgery did not significantly influence these factors in ADC patients.

A recently published randomised controlled trial[31] comparing neoadjuvant chemotherapy followed by surgery with nCRT followed by surgery revealed that patients treated with chemoradiotherapy suffered significantly from more severe complications. Consistent with this finding, we observed that postoperative morbidity in our study was relatively high. Although we observed a trend towards more postoperative events in patients with an extended time interval beyond 8 weeks, postoperative morbidity was not significantly influenced by an increased TTS. This trend may be confounded by a selection bias because patients with a longer waiting period exhibited significantly more comorbidities. Additionally, the study included more ASA III patients and thus reflects the influence of different patient populations. This indicates that we favoured a longer interval based on the patient's condition after completion of the neoadjuvant therapy. However, in our multivariable analysis, comorbidities and ASA III were not significant factors. Shapiro and colleagues[25] made a similar observation wherein an increase in TTS was associated with a longer hospital stay and increased postoperative complications. They also concluded from their analysis that the Charlson comorbidity index, the Karnofsky performance status at the end of nCRT, and weight loss were potential delay-related confounders.

Our findings regarding postoperative complications are consistent with previous studies of SCC patients[17;18;23-26]. However, a study conducted by Wang et al.[27], in which a large population of patients diagnosed with SCC was studied, demonstrated that delaying surgery after nCRT was associated with positive surgical margins and surgical mortality. This observation may be explained by findings from this current study, namely advanced pathological stages were more frequently observed in patients with a time to surgery over 60 days. Delaying surgery after nCRT should not be compared with salvage esophagectomy after definitive CRT (dCRT). A systematic review[32] revealed that postoperative mortality and morbidity are both significantly increased in patients who were treated with dCRT followed by salvage esophagectomy, rather than nCRT followed by a planned esophagectomy. Possible explanations for these differences are the patient's condition (dCRT is often chosen due to the patient's poor performance status) and the higher dose of radiotherapy, which can induce more fibrosis[16] and lead to higher postoperative morbidity.

A pCR was observed in 26.3% of the patients. This finding was consistent with pCR rates for ADC, as described in previous studies[33]. Surprisingly, a non-significant decrease in pCR rate was observed when the TTS increased. Although not significant, this study also revealed more patients with a good response (TRG 1-3) in patients with TTS ≤ 8 weeks. We hypothesize that the clinical condition of patients with a poor response may be worse, which is a valid reason to postpone surgery beyond 8 weeks. However, this needs to be further studied. Data on the influence of delaying TTS on pathologic response rate are conflicting. Some studies revealed no influence on pathologic response[17;18;23;26], whereas others indicated that delaying surgery after nCRT significantly increased the probability of pCR. An increased interval between nCRT and surgery revealed a significantly increased pCR rate in a study conducted by Shaikh and colleagues[24]. However, this study was performed on a relatively small sample size (n = 88), which led to smaller groups for each timeframe. Patients in the study performed by Shapiro and colleagues[25] were treated according to the CROSS protocol[3], which was also used for most patients in our study. Despite using the same neoadjuvant treatment regimen, their study showed that increasing TTS significantly increased the occurrence of pCR. However, in contrast to our study, only a minority of the patients in their study had a TTS beyond 8 weeks, both ADC (77%) and SCC (23%) were included, and tumor histology was not included in their multivariable analysis.

The five-year survival rate in our study was similar for both groups, which is consistent with previous studies demonstrating that delaying surgery beyond the currently accepted timeframe does not have a negative influence on overall survival[17;18;26]. Ruol et al.[23] demonstrated that overall survival increased when TTS was prolonged from 6 weeks to the maximal 13 weeks in a subgroup of patients who underwent R0 resection. This finding may be because only patients with SCC were included in the study. In our study, in which a radical resection was achieved in greater than 90% of the cases, we could not confirm that increasing the interval between nCRT and surgery affected the overall survival. Overall survival, however, is not equivalent to the quality of life (QoL). Although studies demonstrated that nCRT has a temporary negative effect on QoL, one study revealed that QoL was not impaired by nCRT[34]. Given that our patients were not subjected to health-related QoL questionnaires, we were not informed on the course of the QoL in our study.

This study has some limitations that should be taken into consideration. Although all data obtained from this study were collected prospectively and the survival data were updated in a timely manner, it is still a retrospective cohort study and was not randomised. The arbitrary period of 8 weeks was used as a cut-off point based on previous retrospective studies addressing the same issue[15;18]. A different cut-off point may change the outcomes. Another limitation could be the selection bias given that surgery was delayed because of the patient's condition in the majority of cases, demonstrating that decisions were made based on the clinical condition and not on randomised clinical trial regulations. Although the results were adjusted in the multivariable analysis for comorbidities and ASA classification, the lack of randomisation could still influence our results. Furthermore, we were not informed on the histological response when a patient with an extended interval was treated earlier given that histopathological verification only occurred at the time of surgery.

There are many reasons for delaying surgery after nCRT such as logistical and patient related factors like poor physical status, malnutrition or medical conditions like the complications and toxicity of nCRT. Since this study suggest that delaying surgery has no significant effect on postoperative outcome, for some patients delaying surgery after nCRT seems a safe option to improve patients general status or for logistic reasons.

To draw firmer conclusions, prospective randomised trials are necessary. Recently, a prospective single arm feasibility trial named PreSANO[35] was initiated. This study addressed the issue of TTS after nCRT and its effect on clinical and pathologic response. This study could form the basis for a randomised trial to compare planned surgery after nCRT and with surgery as needed, which postpones surgery in patients with a reliable pCR.

In conclusion, our findings suggest that delaying surgery beyond 8 weeks does not affect pathologic response nor does it have a significantly negative impact on postoperative morbidity or overall survival. Our results suggest that it is safe to postpone surgery beyond 8 weeks for patients experiencing serious toxicity following nCRT. On the other hand, it appeared that if the patient is fit for surgery, postponing surgery does not have any additional advantages. Definitive conclusions from a randomised trial are needed to define the optimal TTS and to determine whether a longer TTS is beneficial for patients.

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CHAPTER 8

Radiation dose does not influence anastomotic complications in patients with esophageal cancer treated with neoadjuvant chemoradiation and transhiatal esophagectomy.

Authors:

M. Koëter MD[1]; M.J.C. van der Sangen MD[2]; C.W. Hurkmans PhD[2];
M.D.P. Luyer MD, PhD[1]; H.J.T. Rutten MD, PhD[1]; G.A.P. Nieuwenhuijzen MD, PhD[1]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands.

[2] Department of Radiation Oncology,
Catharina Hospital Eindhoven, The Netherlands

Abstract

Background: Neoadjuvant chemoradiation might increase anastomotic leakage and stenosis in patients with esophageal cancer treated with neoadjuvant chemoradiation and esophagectomy. The aim of this study was to determine the influence of radiation dose on the incidence of leakage and stenosis.

Methods: Fifty-three patients with esophageal cancer received neoadjuvant chemoradiation (23 x 1.8 Gy) (combined with Paclitaxel and Carboplatin) followed by a transhiatal esophagectomy between 2009 and 2011. On planning CT, the future anastomotic region was determined and the mean radiation dose, V20, V25, V30, V35 and V40 were calculated. Logistic regression analysis was conducted to examine determinants of anastomotic leakage and stenosis.

Results: Anastomotic leaks occurred in 13 of 53 patients (25.5%) and anastomotic stenosis occurred in 24 of 53 patients (45.3%). Median follow-up was 20 months. Logistic regression analysis showed that mean dose, V20-V40, age, co-morbidity, method of anastomosis, operating time and interval between last radiotherapy treatment and surgery were not predictors of anastomotic leakage and stenosis.

Conclusions: A radiation dose of 23 x 1.8 Gy on the future anastomotic region has no influence on the occurrence of anastomotic leakage and stenosis in patients with esophageal cancer treated with neoadjuvant chemoradiation followed by transhiatal esophagectomy.

Introduction

Esophageal cancer is the eighth most commonly diagnosed type of cancer worldwide and it is the sixth leading cause of cancer deaths[1]. The incidence of esophageal carcinoma in the Netherlands, especially adenocarcinoma, has rapidly risen from 1731 new cases in 2000 to 2499 in 2010[2]. According to the current Dutch guidelines, the preferred curative treatment for non-metastatic disease is neoadjuvant chemoradiation followed by transhiatal or transthoracic esophagectomy[3]. Patients with an irresectable tumor, or patients who are too vulnerable for surgery are often proposed for definitive chemoradiation which show encouraging results[4;5]

Surgical treatment has an acceptable mortality in high volume centres, but high rates of post-operative morbidity have still been described[6-9]. However, pulmonary complications and anastomotic complications like leakage and stenosis are still common[7-9]. The incidence of anastomotic leakage reported in the literature ranges from 5.7% to 41%[6-16]. Incidence rates of anastomotic stenosis are even higher ranging from 21.8% to 44%[6;10-12].

Factors like co-morbidity, nutrition status, anastomotic location, anastomotic technique and blood loss during surgery are hypothesised to be related to the development of anastomotic leakage and stenosis[10;17].

Neoadjuvant chemoradiation might also play a role in developing anastomotic complications. Studies comparing neoadjuvant chemoradiation followed by surgery with surgery alone showed conflicting results with respect to the risk of anastomotic leakage and stenosis due to the neoadjuvant treatment[8;11;15;16;18]. However, these studies incorporated heterogeneous patient groups, radiation fields and anastomotic locations. A recent study showed that in patients receiving neoadjuvant chemoradiation median radiation dose to the gastric fundus was an independent predictor for early anastomotic complications in patients with an Ivor-Lewis esophagectomy[19]. However in an intrathoracic anastomosis the region below the gastric fundus rather than the gastric fundus itself is used for the anastomosis because a shorter gastric conduit is needed when compared with a cervical anastomosis, raising the question of whether or not other factors are responsible for the observed difference. When compared with an Ivor-Lewis esophagectomy, in patients receiving a transhiatal resection and a cervical anastomosis, a larger part of the irradiated gastric fundus is used for the anastomosis. Hence, the aim of our study was to determine the influence of radiation dose on the incidence of anastomotic complications (leakage and stenosis) in a more homogeneous patient group with distal esophageal or gastro-esophageal junction cancer undergoing neoadjuvant chemoradiation followed by a transhiatal esophagectomy and cervical anastomosis. In all of these patients the fundus of the stomach was irradiated to a varying degree.

Methods

Study population

Between 2009 and 2011 we included 53 consecutive patients with distal esophageal cancer (C15.5) or gastro-esophageal junction cancer (C16.0), who received neoadjuvant chemoradiation followed by an open or laparoscopic transhiatal esophagectomy with a left cervical anastomosis. Median follow-up duration was 20 months (range 0.2-25). All patients had histologically proven adenocarcinoma or squamous cell carcinoma with no evidence of distant metastases (cT1-3, N0-3, M0; TNM 7)[20]. Cancer staging included clinical examination, esophago-gastroscopy with biopsies, endoscopic ultrasonography (EUS), external ultrasonography of the cervical region, computed tomography (CT) of the chest and abdomen and a positron emission tomography fused with CT (PET- CT). This research is reviewed by the local medical ethics committee but the Dutch Medical Research (Human Subjects) Act is not applicable to this study.

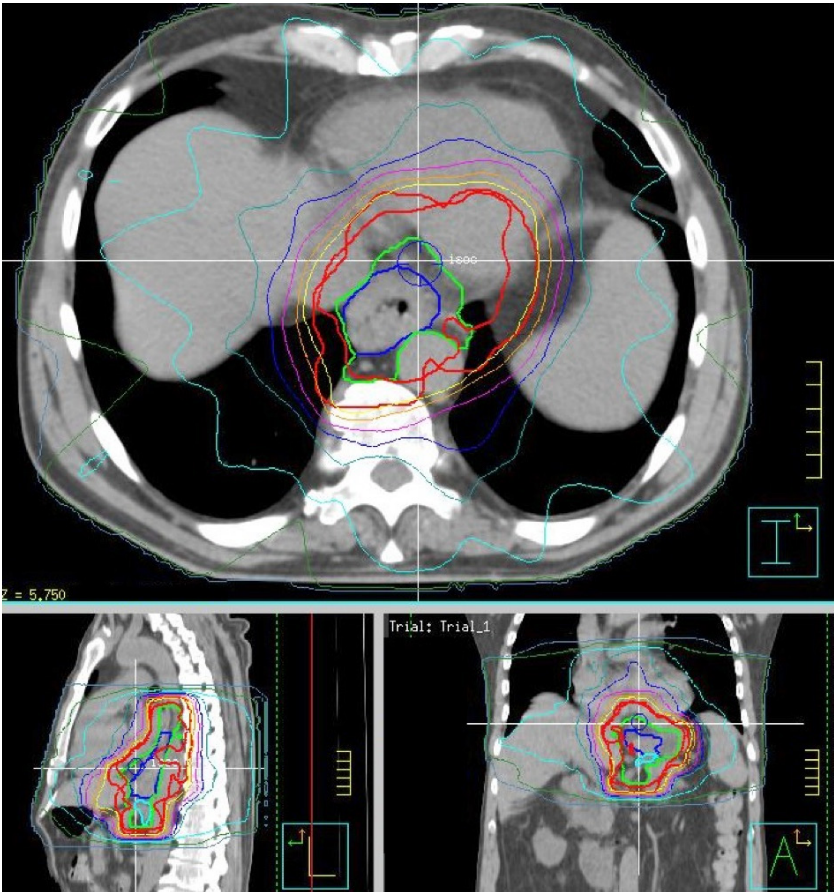
Surgery

Surgical treatment consisted of a laparoscopic or open transhiatal esophagectomy with gastric tube interponate[18]. A left cervical anastomosis was performed (at surgeon's preference) end-to-end with hand-sewn continuous or interrupted sutures or side-to-side with a stapling device (Collard anastomosis[21]).

Neoadjuvant chemoradiation regimen

The neoadjuvant regimen consisted of Three-Dimensional Conformal Radiotherapy (3D-CRT) to a total dose of 41.4 Gy (23 fractions of 1.8Gy, 5 fractions a week) combined with Paclitaxel (50mg/m^2) and Carboplatin (AUC=2) administered by intravenous infusion on days 1, 8, 15, 22 and 29. The Gross Tumor Volume (GTV) included all visible tumor and pathologically enlarged lymph nodes (determined by CT, PET-CT or EUS). The Clinical Target Volume (CTV) was defined by the GTV (node and tumor) plus the area of regional lymph nodes up to at least 3 cm in cranial and caudal extension of the esophagus from the tumor GTV. To ensure adequate margins around the macroscopic tumor, a minimum CTV-GTV margin of 0.5 cm was required. For distal tumors, the caudal margin should follow the wall of esophagus and cardia. The margin in the direction of the wall of the cardia was limited to 2 cm. The Planning Target Volume (PTV) consisted of the CTV plus a margin of 1 cm in all directions (Figure 1). These margins were chosen as these are the margins we use in clinical practice. We realise that these margins should preferably be patient specific and dependent on, for example, the individual tumor motion. Because of these margins, the fundus in all patients with distal or junction tumors was irradiated to a varying degree.

Figure 1. Example pictures of dose distribution.



Blue: GTV, Green: CTV, Red: PTV

Calculation of RT dose to the anastomotic region of interest

The future anastomotic region was retrospectively determined on the preoperative planning CT using the Philips Pinnacle treatment planning system version 9.0. CT slice thickness and separation were 3 mm. The most proximal part of the stomach was determined. From that point, a 5 cm distal (coronal plane) vertical line was drawn. On the transversal plane the distal margin at 7 cm was drawn. We used a 2 cm margin from the lesser curvature and a 2 cm margin from the most proximal part of the stomach (Figure 2). These margins are determined after consultation of the operating surgeon. The future anastomotic region in all patients was determined by the first author.

From this future anastomotic region we calculated the following parameters: volume, mean dose, V20, V25, V30, V35 and V40 (percentage irradiated volume receiving more than respectively 20, 25, 30, 35 and 40 Gy). In order to quantify the effect of a larger CTV-PTV margin on the parameters we repeated the analysis with an expansion of 0.5cm in all directions (anastomotic region volume + 0.5cm)

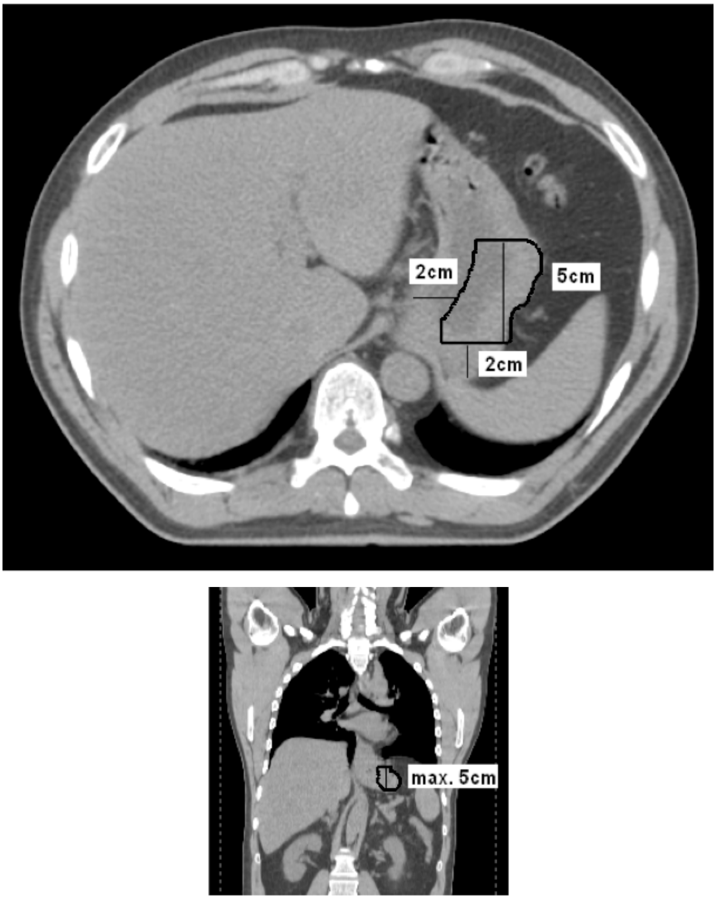
Classification of leakage and stenosis

Anastomotic leakage was defined as any clinical evidence of leakage of salivary fluid in the cervical region, gastric conduit necrosis or evidence of anastomotic leakage on CT or with esophago-gastroscopy (CTCAE grade 1-5)[22]. Anastomotic stenosis was defined as dysphagia for which one or more endoscopic dilatation(s) of the anastomosis was needed.

Statistical analysis

Differences in patient, tumor and dose characteristics between patients with or without anastomotic leakage or anastomotic stenosis were compared using the Mann-Whitney U test and the chi-square test. Univariable and multivariable logistic regression analyses were conducted to evaluate the potential risk factors for developing anastomotic leakage or stenosis. All analyses were performed using Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). All reported p-values below 0.05 were considered statistically significant.

Figure 2. Example of a planning CT in which the future anastomotic region is drawn



Results

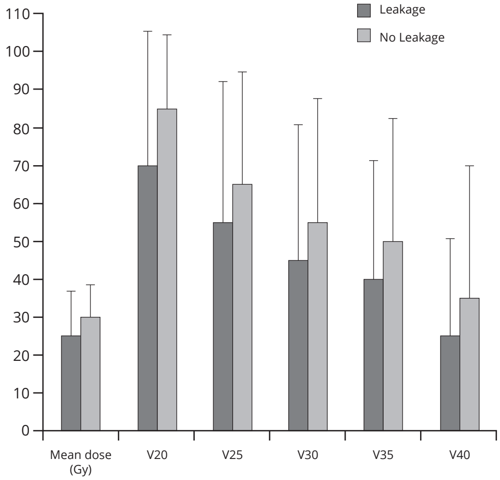
All 53 patients completed the neoadjuvant chemoradiation regimen followed by transhiatal esophagectomy after a therapy free interval of 4-18 weeks, with a median of 9 weeks. The mean irradiation dose to the anastomotic region was 30.3Gy [range 6-42], with a mean volume of 48.2 cm^3 [range 21-92]. Postoperatively, 13 of 53 patients (25.5%) developed an anastomotic leak and six patients (11.3%) needed a surgical re-intervention; of these, 4 patients (7.5%) required re-intervention because of severe anastomotic problems. Two patients needed thoracic drainage for thoracic empyema. In three patients, drainage of a cervical abscess was performed. One patient needed re-intervention for an abdominal dehiscence. Two patients (3.8%) died in hospital: one patient died because of Acute Respiratory Distress Syndrome and another of myocardial infarction. To date, 15 patients (28.3%) have died during follow-up, with median follow-up duration of 20 months. Of these patients, 10 died because of cancer recurrence, 3 patients died from a non-disease-related cause and 2 patients had an unknown cause of dead.

Patients with an anastomotic leakage were hospitalised significantly longer than patients without anastomotic leakage (22 vs. 13 days, $p=0.001$). Between the groups with or without anastomotic leakage no significant differences in age, gender, BMI, co-morbidity, ASA classification, histology, type of operation, duration of the procedure, method of anastomosis, anastomotic region volume, mean dose and time between the end of the neoadjuvant treatment and surgery were observed (table 1). Comparable results on leakage rate were observed using the anastomotic region volume + 0.5 cm. In Figure 3 we depicted the percentage of patients with and without leakage as a function of DVH parameters.

Table 1. Characteristics of patients with or without anastomotic leakage, treated with neo-adjuvant chemoradiation followed by transhiatal esophagectomy.

	Anastomotic leakage		
	Yes (n=13)	No (n=40)	p-value
Mean age	62.4 [41-77]	63.8 [41-82]	0.83
Gender:			
Male (n=49)	13 (27%)	36 (73%)	
Female (n=4)	0 (0%)	4 (100%)	0.56
BMI	27.5 [21-41]	26.4 [19-35]	0.65
Co-morbidity:			
0 (n=13)	3 (23%)	10 (77%)	
1 (n=18)	4 (22%)	14 (78%)	
2 or more (n=22)	6 (27%)	16 (73%)	0.93
ASA classification:			
I (n=8)	3 (38%)	5 (63%)	
II (n=41)	9 (22%)	32 (78%)	
III (n=4)	1 (25%)	3 (75%)	0.65
Histologic type:			
Adenocarcinoma (n=49)	12 (24%)	37 (76%)	
Squamous cell carcinoma (n=4)	1 (25%)	3 (75%)	0.98
Mean volume (cm^3)	53.1 [33-71]	46.6 [21-92]	0.10
Mean dose (Gy)	26.4 [6-41]	31.6 [15-42]	0.16
V20	71.2%	88.3%	0.54
V25	53.8%	66.2%	0.27
V30	45.4%	57.3%	0.24
V35	39.1%	50.3%	0.24
V40	26.2%	36.5%	0.32
OR time (min)	172 [118-329]	187 [134-292]	0.09
Resection type:			
Open (n=21)	7 (33%)	14 (67%)	
Laparoscopic (n=32)	6 (19%)	26 (81%)	0.23
Method of anastomosis:			
End-to-end continuous (n=33)	6 (18%)	27 (82%)	
End-to-end interrupted (n=11)	4 (36%)	7 (64%)	
Side-to -side stapler (n=9)	3 (33%)	6 (67%)	0.38
Interval last RT– surgery (days)	70 [40-127]	69 [31-121]	0.87
Hospital stay (days)	22 [13-71]	13 [6-35]	0.001

Figure 3. Percentage of patients with and without leakage as a function of DVH parameters. Error bars represent 1 SD.

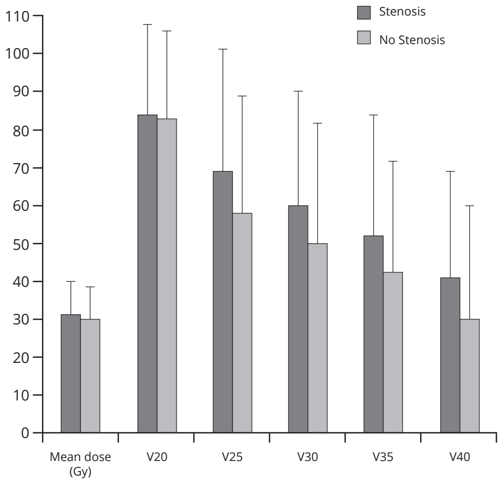


Clinically, anastomotic stenosis occurred in 24 of 53 patients (45.3%). Between the groups with or without anastomotic stenosis, no significant differences in age, gender, BMI, co-morbidity, ASA classification, histology, type of operation, operating time, method of anastomosis, anastomotic region volume, mean dose and time between the end of the neoadjuvant treatment and surgery were observed (table 2). Comparable results on stenosis rate were observed using the anastomotic region volume +0.5 cm. In Figure 4 we depicted the percentage of patients with and without stenosis as a function of DVH parameters.

Table 2. Characteristics of patients with or without anastomotic stenosis, treated with neo-adjuvant chemoradiation followed by transhiatal esophagectomy.

	Anastomotic stenosis		
	Yes (n=24)	No (n=29)	p-value
Mean age	61.3 [41-78]	65.4 [48-82]	0.30
Gender:			
Male (n=49)	21 (43%)	28 (57%)	
Female (n=4)	3 (75%)	1 (25%)	0.32
BMI	26.6 [19-41]	26.7 [21-35]	0.68
Co-morbidity:			
0 (n=13)	9 (69%)	4 (31%)	
1 (n=18)	8 (44%)	10 (56%)	
2 or more (n=22)	7 (32%)	15 (68%)	0.10
ASA classification:			
I (n=8)	4 (50%)	4 (50%)	
II (n=41)	19 (46%)	22 (54%)	
III (n=4)	1 (25%)	3 (75%)	0.69
Histologic type:			
Adenocarcinoma (n=49)	22 (45%)	27 (55%)	
Squamous cell carcinoma (n=4)	2 (50%)	2 (50%)	0.84
Volume (cm^3)	48.3 [29-81]	48.1 [21-92]	0.92
Mean dose (Gy)	31.2 [6-42]	29.6 [8-42]	0.38
V20	84.9%	83.4%	0.27
V25	68.8%	58.5%	0.24
V30	59.5%	50.1%	0.30
V35	52.9%	43.1%	0.28
V40	40.1%	28.8%	0.14
OR time (min)	184 [118-329]	182 [138-292]	0.75
Resection type:			
Open (n=21)	11 (52%)	10 (48%)	
Laparoscopic (n=32)	13 (41%)	19 (59%)	0.40
Method of anastomosis:			
End-to-end continuous (n=33)	15 (45%)	18 (55%)	
End-to-end interrupted (n=11)	7 (64%)	4 (36%)	
Side-to -side stapler (n=9)	2 (22%)	7 (78%)	0.18
Interval last RT– surgery (days)	65 [37-118]	73 [31-127]	0.31
Hospital stay (days)	14 [6-35]	16 [6-71]	0.63
Anastomotic leakage (n=13)	7 (54%)	6 (46%)	0.48

Figure 4. Percentage of patients with and without stenosis as a function of DVH parameters. Error bars represent 1 SD.



Univariable logistic regression analysis showed that mean radiation dose was a borderline significant predictor for anastomotic leakage. In addition univariable analysis also showed that patients with a high V20 percentage were less likely to develop anastomotic leakage. However, multivariable analysis showed that V20 percentage and mean dose to the proposed area of the anastomosis were not significant predictors for anastomotic leakage anymore. Again, all other factors like age, BMI, co-morbidity (including cardiovascular and pulmonary co-morbidity separately), histology, ASA classification, type of resection, operating time, method of anastomosis, mean dose, V25-V40 and interval between the end of the neoadjuvant treatment and surgery were not significant predictors for anastomotic leakage in our univariable analysis and were therefore not analysed in the multivariable analysis (table 3). Furthermore, the same analyses for the anastomotic region volume + 0.5 cm had no influence on the results.

Table 3. Predictors of anastomotic leakage in patients with distal esophageal or esophago-gastric junction cancer treated with neoadjuvant chemoradiation followed by transhiatal esophagectomy.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.99	0.93-1.05	0.63			
BMI	1.07	0.91-1.24	0.42			
Co-morbidity:						
0	0.80	0.16-3.94	0.78			
1	0.76	0.18-3.26	0.71			
2 or more	ref					
Cardiovascular co-morbidity:						
No	1.29	0.37-4.53	0.69			
Yes	ref					
Pulmonary co-morbidity:						
No	ref					
Yes	1.7	0.36-8.04	0.50			
ASA classification:						
I	2.13	0.43-10.68	0.36			
II	ref					
III	1.19	0.11-12.82	0.89			
Histology:						
Adenocarcinoma	ref					
Squamous cell carcinoma	0.98	0.10-10.83	0.98			
Mean Dose	1.00	1.00-1.00	0.07	1.00	1.00-1.00	0.67
V20	0.97	0.96-1.00	0.03	0.96	0.90-1.02	0.21
V25	0.99	0.97-1.01	0.23			
V30	0.99	0.98-1.01	0.25			
V35	0.99	0.97-1.01	0.28			
V40	0.99	0.97-1.01	0.32			
OR time	0.99	0.97-1.01	0.25			
Resection type:						
Open	2.17	0.61-7.71	0.23			
Laparoscopic	ref					
Method of anastomosis:						
EE continuous	ref					
EE interrupted	2.57	0.57-11.69	0.22			
Side-to -side stapler	2.25	0.44-11.65	0.33			
Interval last RT- surgery	1.00	0.83-1.20	0.99			

Univariable analysis showed that age and interval between the end of the neoadjuvant treatment and surgery were borderline significant. Anastomotic stenosis developed significantly more often in patients without comorbidity compared with patients with >=1 comorbidity. However, multivariable analysis showed that factors such as age, co-morbidity and interval between radiotherapy dose and surgery were not significant predictors for anastomotic stenosis. All other factors like BMI, cardiovascular and pulmonary co-morbidity, histology, ASA classification, type of operation, operating time, method of anastomosis, mean dose, and V20-V40 were not significant predictors for anastomotic stenosis in our univariable analysis and were therefore not analysed in the multivariable analysis (table 4). Again, the same analyses for the ROI + 0.5 cm had no influence on the results observed in our analysis.

Table 4. Predictors of anastomotic stenosis in patients with distal esophageal or esophago-gastric junction cancer treated with neoadjuvant chemoradiation followed by transhiatal esophagectomy.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.96	0.90-1.01	0.14	0.99	0.92-1.06	0.66
BMI	0.99	0.87-1.14	0.92			
Co-morbidity:						
0	4.82	1.10-21.19	0.04	3.17	0.54-18.82	0.20
1	1.71	0.77-6.24	0.41	1.39	0.34-5.67	0.64
2 or more	ref					
Cardiovascular co-morbidity:						
No	2.73	0.89-8.33	0.78			
Yes	ref					
Pulmonary co-morbidity:						
No	ref					
Yes	0.96	0.23-4.06	0.96			
ASA classification:						
I	1.16	0.25-5.72	0.85			
II	ref					
III	0.39	0.04-4.03	0.43			
Histology:						
Adenocarcinoma	ref					
Squamous cell carcinoma	1.23	0.16-9.43	0.84			
Mean dose	1.00	1.00-1.00	0.50			
V20	1.00	0.98-1.03	0.81			
V25	1.01	0.99-1.03	0.24			
V30	1.01	0.99-1.03	0.28			
V35	1.01	0.99-1.03	0.27			
V40	1.01	0.99-1.03	0.21			
OR time	1.00	0.99-1.01	0.87			
Resection type:						
Open	1.61	0.53-4.88	0.40			
Laparoscopic	ref					
Method of anastomosis:						
EE continuous	ref					
EE interrupted	2.10	0.51-8.57	0.30			
Side-to -side stapler	0.34	0.06-1.90	0.22			
Interval last RT- surgery	0.88	0.74-1.04	0.14	0.92	0.77-1.11	0.39
Anastomotic leakage	1.58	0.45-5.55	0.48			

Discussion

In this study we determined the influence of radiation dose in the future anastomotic region on developing anastomotic leakage and stenosis in patients with distal esophageal or esophago-gastric junction cancer (cT1-3, N0-3, M0) treated with neoadjuvant chemoradiation followed by transhiatal esophagectomy with gastric tube reconstruction and a left cervical anastomosis. Overall, 25.5% of patients developed anastomotic leakage and 45.3% developed anastomotic stenosis. Our study identified no significant predictors of anastomotic leakage and stenosis. In contrast with a recent study[19], radiation dose did not have a significant influence on developing anastomotic leakage and stenosis.

This study shows that variations in mean dose and V20 until V40 had no significant influence on developing anastomotic leakage. However, a recent study demonstrated that the mean radiation dose on the gastric fundus dose was an independent predictor for early anastomotic complications like leakage[19]. The recent study had a different neoadjuvant treatment regime (36 Gy in 20 fractions combined with 5-FU and cisplatin) and a different surgical procedure (Ivor-Lewis) compared with the current study. Although the authors did not describe their surgical procedure in detail, the region below the gastric fundus at the level of the watershed of the gastroepiploic vessels is most commonly used for the intra-thoracic anastomosis in the Ivor-Lewis procedure. In a cervical anastomosis, the gastric tube should be longer and the anastomosis reconstructed from the fundus region of the stomach. Hence, the radiation dose on the future anastomotic region could even be less than the dose suggested by the authors and other factors could potentially be more responsible for the observed effects than the irradiation on the gastric fundus itself. Therefore, it is even more remarkable that we did not observe a negative effect of irradiation to the fundus on anastomotic complications in our series. Furthermore, the authors did not have a clear definition of anastomotic leakage; in addition, their description of the determined anastomotic region was not clear and not reproducible.

In our study, variations in mean dose and V20-V40 showed no significant influence on developing anastomotic stenosis. This is in concordance with a study in which it was demonstrated that neoadjuvant chemoradiation was not a predictor for the incidence of benign anastomotic strictures. However, this study did show that neoadjuvant chemoradiation was an independent predictor for patients with refractory strictures (requiring >10 dilatations)[18]. Furthermore, a recent study showed a higher mean radiation dose in patients with anastomotic stenosis[19].

Comorbidity in our study did not have an influence on the development of anastomotic leakage or stenosis. This is in concordance with another study showing that major co-morbidity is not an independent predictor for early anastomotic complications like leakage[19]. Another study confirmed these results and showed that diabetes, chronic obstructive pulmonary disease and coronary artery disease had no influence on developing anastomotic leakage[8].

Anastomotic leakage rates vary between studies, with leakage rates between 5.7 and 41%[6-16]. This might be the result of the various definitions of anastomotic leakage. Some studies define leakage as clinical or radiological evidence of leakage. However, other definitions include only clinical leakage or anastomotic leakage requiring re-intervention. In this study, anastomotic leakage was defined as every evidence of leakage (including all clinical and radiologic evidence of leakage), explaining the relatively high rate of anastomotic leakage (25.5%) in our study compared with others[6-15]. As summarised in table 5, randomized controlled trials that have compared neo-adjuvant chemoradiation with subsequent surgery versus surgery alone show different results with regard to the incidence of anastomotic leakage and the influence of chemoradiation on leakage rate. The incidence of leakage rates in those RCTs ranged from 3% to 30%. The influence of neo-adjuvant chemoradiation on leakage rate is often not statistically tested. Furthermore, the differences in leakage rate between patients receiving neo-adjuvant chemoradiation with surgery vs. surgery alone are small. When comparing our leakage rate with the rate reported in a recent Dutch multicentre randomized trial studying the role of neo-adjuvant chemoradiation with the same regime as our study, our leakage rate appears to be comparable[16].

The influence of (chemo)radiation on anastomotic leakage has also been studied in other solid tumors like rectal cancer. A large randomized and a large retrospective study showed that neo-adjuvant chemoradiation did not influence anastomotic leakage rates following Total Mesorectal Excision in patients with rectal cancer[23;24]. Another large Dutch Multicentre RCT showed no difference in anastomotic leakage rates between patients who received short course neoadjuvant radiotherapy followed by surgery compared to surgery alone. However, they did observe significantly more post-operative wound complications in the radiotherapy group[25].

Anastomotic stenosis occurred in 45.3% of the patients; however, other studies have shown a lower incidence (21.8-41.7%)[6;11;12;18]. As shown in table 5, anastomotic stenosis is often not registered in randomized controlled trials. Only two studies mention anastomotic stenosis, and show no significant differences between chemoradiation with subsequent surgery vs. surgery alone. The incidence of anastomotic stenosis in this study is relatively high; however, it is in concordance with a study in which the incidence of anastomotic stricture was 44% in patients with an end-to-end anastomosis[10].

Anastomotic leakage was not a predictor for anastomotic stenosis in our study. This is not supported by other studies in which anastomotic leakage was found to be an independent predictor for anastomotic stenosis[11;12;18]. This difference might be a result of the relatively small number of patients and the relatively high anastomotic leakage rate identified in the current study.

Other factors besides chemoradiation that might influence anastomotic problems are, according to the literature, type of resection (transthoracic vs. transhiatal) and location of anastomosis (thoracic vs. cervical)[6;10;17]. In the studied RCTs, both types of surgery have been often used and anastomotic location was mostly cervical or not mentioned at all (Table 5). Based on these heterogeneous RCTs, it is difficult to determine factors that influence anastomotic leakage and stenosis. Therefore, we investigated a homogenous patient population with the same type of resection and a strictly defined cervical anastomotic location.

This study is unique, but also has some limitations. The study population is relatively small; however, the group used here is more homogenous than others with respect to the uniform treatment and type of anastomosis. Furthermore, the determination of the future anastomotic region, despite the consultation with the consulting surgeon, may be prone to a certain degree of subjective variability. However, since we have uniformly determined the anastomotic region within a pre-defined distance from the most proximal part of the stomach, we believe that the comparison between groups is accurate enough to draw firm conclusions from the results.

Furthermore, we were not able to compensate breathing-induced organ motion. This could have influenced the calculated dose to the region of interest. However because the PTV consisted of the CTV plus a margin of 1 cm in all directions we do not think this will have a significant influence on our results. As in other studies looking at the correlation between radiation induced morbidity and anastomotic complications, the influence of day-to-day treatment variations on the dose to the region could not be quantified as we do not have CBCT imaging data of these patients, which is a clear limitation. Realising this, it is even more striking that we did not observe a correlation between dose and morbidity, as including day-to-day variations will only blur the dose distributions we want to correlate with morbidity even more. In this study we did not measure esophagitis grade after chemoradiation. Recent study in lung cancer patients showed association between higher V50 and esophagitis[26]. The number of patients with esophagitis in our study will be comparable with recent published results from the CROSS II trial with the same chemoradiation regimen. They observed that 19% of the patients developed esophagitis[16].

Table 5. Anastomotic complications in randomised trials comparing neo-adjuvant chemoradiation and surgery with surgery alone.

Anastomotic complications neo-adjuvant chemoradiation and surgery vs. surgery alone										
Study	**Groups No**		**CRT Scheme**		**Surgery Type**	**Anastomotic Location**	**Anastomotic Leakage**		**Anastomotic Stenosis**	
	CRT+S	**S**	**Chemo**	**RT**			**CRT+S**	**S**	**CRT+S**	**S**
Nygaard et al. 1992 [27]	34	38	Cisplatin	35.0 Gy (20x1.75)	TTE	Not mentioned	6%	3%	Not Mentioned	
Le Prise et al. 1993 [28]	41	45	Cisplatin 5-FU	20.0 Gy (10x2.0)	Not mentioned	Not mentioned	Not Mentioned		Not Mentioned	
Walsh et al. 1996 [29]	58	55	Cisplatin 5-FU	40.0 Gy (15x2.67)	TTE or THE	Cervical	3%	4%	Not Mentioned	
Bosset et al. 1997 [30]	143	139	Cisplatin	37.0 Gy (10x3.7)	TTE >80%	Not mentioned	Not Mentioned		Not Mentioned	
Lee et al. 2004 [31]	51	50	Cisplatin 5-FU	45.6 Gy (38x1.2)	TTE	Cervical	Not Mentioned		14%	17%
Urba et al. 2001 [32]	50	50	Cisplatin 5-FU Vinblastin	45.0 Gy (30x1.5)	THE	Cervical	15%	8%	Not Mentioned	
Burmeister et al. 2005 [33]	128	128	Cisplatin 5 FU	35.0 Gy (15x2.3)	TTE	Thoracic or Cervival	5%	5%	19%	24%
Tepper et al. 2008 [34]	30	26	Cisplatin 5-FU	50.4 Gy (28x1.8)	TTE or THE	Not mentioned	Not Mentioned		Not Mentioned	
Van Hagen et al. 2012 [16]	178	188	Carboplatin Paclitaxel	41.4 Gy (23x1.8)	TTE or THE	Cervical	22%	30%	Not Mentioned	

In conclusion, this study demonstrates that radiation dose on the future anastomotic region did not have a significant influence on the occurrence of anastomotic leakage and stenosis in patients with esophageal cancer treated with this commonly used regimen of neoadjuvant chemoradiation followed by transhiatal esophagectomy and left cervical anastomosis. Although with a relative small study population, our study is important for clinical practice since it suggests that radiation to the future anastomotic region within a regimen of neo-adjuvant chemoradiation with a moderate total dose has no apparent negative effect of anastomotic complications.

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CHAPTER 9

Influence of the extent and dose of radiation on complications after neoadjuvant chemoradiation and subsequent esophagectomy with gastric tube reconstruction with a cervical anastomosis

Authors:

M. Koëter MD[1]; N. Kathiravetpillai MD[1]; J.A. Gooszen MD[2];
M.I. van Berge Henegouwen MD, PhD[2]; S.S. Gisbertz MD, PhD[2];
M.J.C. van der Sangen MD, PhD[3]; M.D.P. Luyer MD, PhD[1];
G.A.P. Nieuwenhuijzen MD, PhD[1]; M.C.C.M. Hulshof MD, PhD[4]

Affiliation:

[1] Department of Surgery,
Catharina Hospital Eindhoven, The Netherlands.

[2] Department of Surgery,
Academic Medical Centre Amsterdam, The Netherlands

[3] Department of Radiation Oncology,
Catharina Hospital Eindhoven, The Netherlands

[4] Department of Radiation Oncology,
Academic Medical Centre Amsterdam, The Netherlands

Abstract

Background: The influence of the extent and dose of radiation on complications was investigated in patients with esophageal cancer treated with neoadjuvant chemoradiation and subsequent esophagectomy with gastric tube reconstruction with a cervical anastomosis**.**

Methods: Between 2005 and 2012, 364 consecutive patients with esophageal cancer treated with neoadjuvant chemoradiation (41.4 Gy combined with chemotherapy) followed by esophagectomy were included. The future anastomotic region in the fundus was determined and the mean dose, V20-V40, upper planning target volume (PTV) border in relation to mediastinal length expressed as the mediastinal ratio were calculated.

Results: Anastomotic leakage (AL) occurred in 22% and anastomotic stenosis (AS) in 41%. Logistic regression analysis revealed no influence of age, comorbidity, mean fundus dose, V20-V40, or the mediastinal ratio on the incidence of AL or AS. In 28% of the patients severe complications (Clavien-Dindo score of ≥ IIIB) occurred. The presence of multiple co-morbidities (HR 2.4 [CI 1.3-4.5], p=0.006) and a mediastinal ratio of 0.5-1.0 (HR 1.9 [CI 1.0-3.5], p=0.036) were both independent predictors of severe complications.

Conclusions: With a mean radiation dose of 24.2 Gy to the future anastomotic region of the gastric fundus, the radiation dose was not associated with the incidence of anastomotic leakage or anastomotic stenosis. The incidence of severe complications was associated with a high superior mediastinal PTV border.

Introduction

The incidence of esophageal cancer in the Netherlands has increased in the past two decades, especially that of adenocarcinomas[1]. The preferred treatment for non-metastatic esophageal cancer in the Netherlands is neoadjuvant chemoradiation followed by transhiatal or transthoracic esophagectomy[2]. Survival in the Netherlands has improved over the past ten years due to multiple factors; however, the introduction of neoadjuvant therapy is regarded as one of the most important factors[3].

Esophageal surgery still has high morbidity rates with anastomotic complications, such as leakage, stenosis, and pulmonary complications. Several factors, such as co-morbidity presence, nutritional status, anastomotic location, anastomotic technique, and atherosclerotic vascular condition, are hypothesized to influence anastomotic leakage and stenosis[4-6]. Neoadjuvant chemoradiation may also serve as a factor in the development and severity of anastomotic complications. A recent study revealed that the median radiation dose to the gastric fundus was a predictor of anastomotic leakage in patients treated with an Ivor-Lewis esophagectomy and intra-thoracic anastomosis[7]. However, another study showed no influence of radiation dose to the future anastomotic region on the occurrence of anastomotic leakage in patients treated with transhiatal esophagectomy and cervical anastomosis[8].
Two meta-analyses revealed no difference in mortality and postoperative morbidity in patients treated with neoadjuvant chemoradiation and surgery compared with surgery alone[9;10]. However, neoadjuvant chemoradiation may influence postoperative pulmonary complications[11;12]. Recently, it was shown in a small series that neoadjuvant chemoradiation did not affect the incidence of postoperative complications, but the severity of postoperative complications was significantly affected[13].

Thus, the aim of our study was to determine, in a large series, the influence of the extent and dose of radiation to the fundus of the stomach and mediastinum on the development and severity of anastomotic complications in patients with esophageal cancer treated with neoadjuvant chemoradiation followed by esophagectomy with cervical anastomosis.

Methods

Study population

Between 2005 and 2012, 364 consecutive patients diagnosed in the Catharina Hospital Eindhoven (n=113) and the Academic Medical Centre Amsterdam (n=251) with esophageal cancer who received neoadjuvant chemoradiation followed by an esophagectomy with cervical anastomosis were included. All patients had a histologically proven tumor with no evidence of irresectability or distant metastases (cT1-4, N0-3, M0; TNM 7[14]). Cancer staging included clinical examination, esophagogastroscopy with biopsies, external ultrasonography (or computed tomography (CT)) of the cervical region, CT of the chest and abdomen, and endoscopic ultrasound when appropriate. Information on medical history and co-morbidity was based on a modified list of the Charlson co-morbidity index[15]. This research was reviewed by the local medical ethics committee.

Surgery

Surgical treatment consisted of an open or minimally invasive transhiatal or transthoracic esophagectomy with a gastric tube reconstruction and cervical anastomosis. Reconstructions with an intrathoracic anastomosis were excluded. The type of surgical treatment was chosen at the surgeon's discretion.

Neoadjuvant chemoradiation regimen

The neoadjuvant regimen consisted of three-dimensional conformal radiotherapy (3D-CRT) with a total dose of 41.4 Gy (23 fractions of 1.8 Gy, 5 fractions a week) combined with chemotherapy. The most commonly used chemotherapy scheme was paclitaxel (50 mg/m2) and carboplatin (area under the curve [AUC]=2) administered by intravenous infusion on days 1, 8, 15, 22, and 29. A minority of the patients received other chemotherapy schemes in ongoing clinical trials. The gross tumor volume (GTV) included the primary tumor and pathologically enlarged lymph nodes. The clinical target volume (CTV) was defined as the GTV (nodes and tumor) plus the area of regional lymph nodes up to at least 3 cm from the GTV in the cranial and caudal extension of the esophagus. For distal and gastro-esophageal (GE) junction tumors, the lymph node area along the left gastric artery (lesser curvature) was always included in the CTV. A minimum GTV-CTV esophageal margin of 0.5 cm was prescribed in the transverse direction. For distal tumors, the caudal margin followed the wall of the esophagus and cardia. The margin in the direction of the wall of the cardia was limited to 2 cm. The planning target volume (PTV) consisted of the CTV plus a margin of 1 cm in all directions. The set up accuracy was standard verified by Cone beam CT scan imaging on day 1,2 and 3 of radiation treatment and thereafter once weekly, with an off-line correction protocol. If set up corrections were necessary, this was always followed by 3 days of extra cone beam CT verifications.

Calculation of RT dose to the anastomotic region of interest

The future anastomotic region was retrospectively determined on the preoperative planning CT using the Philips Pinnacle treatment planning system version 9.2 or the Nucletron Oncentra External Beam planning system version 4.5. The CT slice thickness and separation were 3 and 2.5 mm, respectively. The most proximal part of the stomach was determined. From that point, a 5-cm distal (coronal plane) vertical line was drawn. On the transverse plane, the distal margin at 7 cm was drawn. We used a 2-cm margin from the lesser curvature and a 2-cm margin from the most proximal part of the stomach (Figure 1). These margins were determined after surgical consultation. The future anastomotic region in all patients was determined by the first and second author. From this future anastomotic region, we calculated the following parameters: volume, mean dose, V20, V25, V30, V35, and V40 (percentage of irradiated volume of the fundus receiving equal or more than 20, 25, 30, 35, and 40 Gy, respectively). Since a leakage of a cervical anastomosis often has a mediastinal manifestation, radiation to the mediastinal field may have an impact on the incidence and severity of the sequelae of a cervical leakage. In order to determine the upper PTV border in relation to the mediastinal field we introduced the mediastinal ratio as a relative ratio which is not dependent on the absolute dimensions of the patient. The mediastinal ratio is calculated as the distance between the diaphragm and upper border of the PTV (PTV-top) divided by the distance between the diaphragm and the manubrium-sternal joint (sternal angle) which corresponds with the level of the carina. We divided our patients in three groups: a group with a mediastinal ratio of < 0.5 (diafragm to halfway of the carina), a group with a mediastinal ratio of 0.5-1.0 (halfway of the carina to the carina) and a group with a mediastinal ratio ≥ 1.0 (above the carina).

Classification of complications

Anastomotic leakage was defined as any clinical evidence of leakage of salivary fluid in the cervical region, gastric conduit necrosis, or evidence of anastomotic leakage on CT or with esophago-gastroscopy (Common Terminology Criteria for Adverse Events (CTCAE) grade 1-5)[16]. Anastomotic stenosis was defined as dysphagia for which one or more endoscopic dilatation(s) were needed. Complications were scored using the Clavien-Dindo classification. A severe complication was defined as any complication with a Clavien-Dindo classification of IIIB or higher at admission[17].

Figure 1. Schematic representation of the region of interest representing the future anastomotic region (A). Example of a planning CT on which the future anastomotic region is drawn according to these rules (B).

Figure 1A.

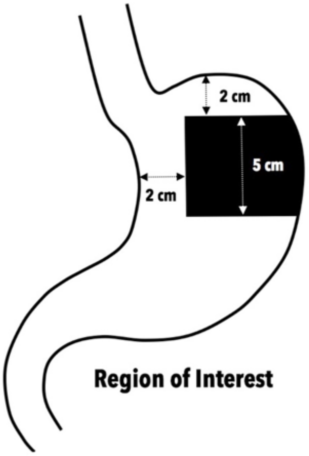
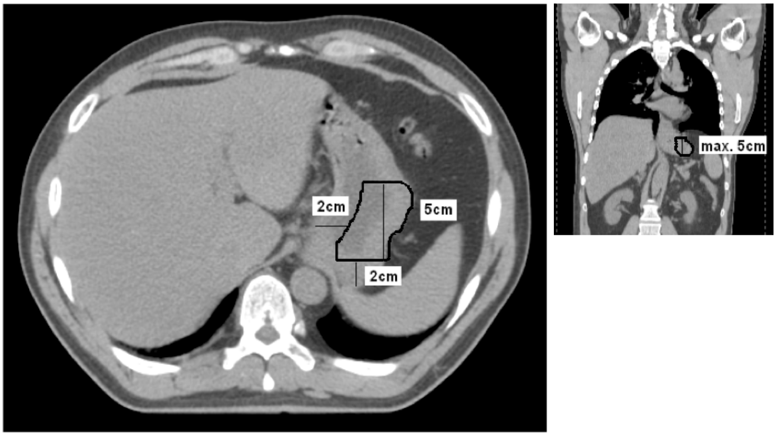


Figure 1B.



Statistical analysis

Univariate and multivariate logistic regression analysis were performed to determine predictors (age, gender, body mass index (BMI), co-morbidity, histology, location, mean dose, V20-40, mediastinal ratio, and type of surgery) of developing anastomotic leakage or stenosis and a complicated postoperative course with Clavien-Dindo IIIB complications or higher. In the multivariate analysis, we included factors with a p-value below 0.1 in the univariate analysis. All analyses were performed using Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Reported p-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

The mean age of the study population was 64 years (SD 8.9), and 80% of the individuals were male. Most tumors were adenocarcinomas (76%) located distally in the esophagus. Transthoracic esophagectomy was performed in 62.1% of the patients, and transhiatal esophagectomy was performed in 37.9% of the patients. A minimally invasive resection was performed in 51.6% of the cases. The mean radiation dose to the anastomotic region was 24.2 Gy (SD 11.8). Mean mediastinal ratio was 0.6 (SD 0.2). The postoperative in-hospital mortality rate was 4.7% (Table 1), and the median follow-up duration for this study was 23 months (range 1-121).

Anastomotic leakage

Anastomotic leakage (CTCAE grade 1-5) occurred in 78 (22%) of 351 patients. The univariate logistic regression analysis revealed no significant influence of age, gender, co-morbidity, BMI, tumor location, or surgery type on postoperative anastomotic leakage. Furthermore, the mean dose, V20-V40 and mediastinal ratio revealed no significant influence on anastomotic leakage. Univariate analysis revealed that squamous cell carcinoma was a significant predictor of anastomotic leakage (hazard ratio (HR) 2.3 [confidence interval (CI) 1.3-4.0], p=0.005). Since histology was the only significant predictor and no other variables had a p-value below 0.1 a multivariate analysis was therefore not performed (Table 2).

Table 1. Characteristics of patients diagnosed with esophageal carcinoma and treated with neoadjuvant chemoradiation followed by esophagectomy with gastric tube reconstruction with a left cervical anastomosis (n=364).

Age (years)	63.6 (SD 8.9)
Gender	
Male	290 (79.7%)
Female	74 (20.3%)
cT stage	
T1	2 (0.5%)
T2	48 (13.2%)
T3	292 (80.2%)
T4	10 (2.7%)
Tx	12 (3.3%)
cN stage	
N0	76 (20.9%)
N1	172 (47.3%)
N2	90 (24.7%)
N3	7 (1.9%)
Nx	19 (5.2%)
BMI	25.7 (SD 4.2)
Co-morbidity	
0	108 (29.7%)
1	141 (38.7%)
2 or more	115 (31.6%)
Tumor location	
Mid	46 (12.6%)
Distal	238 (65.4%)
GEJ	80 (22%)
Histology	
Adenocarcinoma	276 (75.8%)
Squamous cell	75 (20.6%)
Other/unknown	13 (3.6%)
Type of surgery	
Open transthoracic	86 (23.6%)
Open transhiatal	90 (24.7%)
Laparoscopic transhiatal	48 (13.2%)
Hybrid (thoracoscopy/laparotomy)	27 (7.4%)
Complete minimally invasive	113 (31.0%)
Mean fundus dose	24.2 Gy (SD 11.8)
Mean mediastinal ratio	0.6 (SD 0.2)
In-hospital mortality	4.7%
Median length of admission (days)	13.0 (SD 19.8)

Table 2. Univariate logistic regression analysis of anastomotic leakage (n=351).

	Univariate analysis		
	OR	95% CI	p-value
Age			
<70 (n=274)	1.0		
≥70 (n=77)	0.8	0.4-1.5	0.513
Gender			
Male (n=280)	1.0		
Female (n=71)	1.5	0.8-2.7	0.179
BMI	1.0	0.9-1.1	0.975
Co-morbidity			
0 (n=104)	1.0		
1 (n=135)	0.9	0.5-1.7	0.717
2 or more (n=112)	1.4	0.7-2.6	0.334
Histology			
Adenocarcinoma (n=261)	1.0		
Squamous cell carcinoma (n=74)	2.3	1.3-4.0	0.005
Other (n=13)	0.8	0.2-3.6	0.745
Tumor location			
Mid (n=46)	1.8	0.9-3.5	0.112
Distal (n=231)	1.0		
GEJ (n=74)	0.8	0.4-1.5	0.452
Mean dose	1.0	1.0-1.0	0.133
V20 per 10%*	1.0	0.9-1.0	0.437
V25 per 10%*	1.0	0.9-1.1	0.692
V30 per 10%*	1.0	0.9-1.1	0.501
V35 per 10%*	1.0	0.9-1.1	0.574
V40 per 10%*	1.0	0.9-1.1	0.669
Mediastinal ratio[#]			
<0.5 (n=107)	1.0		
0.5-1.0 (n=213)	1.4	0.8-2.6	0.242
≥1.0 (n=28)	1.9	0.7-4.8	0.207
Type of surgery			
Transthoracic (n=83)	0.8	0.4-1.7	0.635
Transhiatal (n=86)	0.9	0.4-1.7	0.686
Laparoscopic transhiatal (n=48)	1.1	0.5-2.4	0.825
Thoracoscopic/laparotomy (n=27)	0.9	0.3-2.6	0.900
Thoracoscopic/laparoscopic (n=107)	1.0		

*Odds ratios displayed in steps of 10%.

[#] Exclusion of 3 missings.

Anastomotic stenosis

Anastomotic stenosis requiring one or more dilatation(s) was observed in 149 patients (41%). The univariate logistic regression analysis indicated that age, gender, BMI, co-morbidity, histology, tumor location, mean dose, V20-V40, type of surgery, and anastomotic leakage were not significantly associated with the development of anastomotic stenosis. Multivariate analysis revealed that only patients with a mediastinal ratio of 0.5-1.0 were less likely to develop anastomotic stenosis (HR 0.6 [CI 0.4-1.0], p=0.036) (Table 3).

Clavien-Dindo ≥ IIIB and mortality

A total of 102 patients (28%) had severe complications with a Clavien-Dindo classification ≥ IIIB. Univariate analysis revealed that age, gender, BMI, tumor location, V20-V40, and resection type had no significant influence on the incidence of a complicated course with complications Clavien-Dindo ≥ IIIB. The presence of multiple co-morbidities, squamous cell histology, mean dose, and mediastinal ratio 0.5-1.0 or ≥1.0 had a significant influence on the incidence of complications with Clavien-Dindo ≥ IIIB. Multivariate analysis revealed that the presence of multiple co-morbidities (HR 2.4 [CI 1.3-4.5], p=0.006) and a mediastinal ratio 0.5-1.0 (HR 1.9 [CI 1.0-3.5], p=0.036) were independent predictors of complications with Clavien-Dindo ≥ IIIB (Table 4). Similar results were obtained when using the median of 0.6 as a cut-off point in the analysis. No significant difference were observed on postoperative in-hospital mortality between patients with mediastinal ratio < 0.5 vs. mediastinal ratio 0.5-1.0 vs. mediastinal ratio ≥ 1.0 (3.5% vs. 5.5% vs. 3.6%, p=0.692).

Table 3. Univariate and multivariate logistic regression analysis of anastomotic stenosis (n=361).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age						
<70 (n=282)	1.0					
≥70 (n=79)	1.1	0.7-1.8	0.719			
Gender:						
Male (n=289)	1.0					
Female (n=72)	1.1	0.7-1.9	0.646			
BMI	1.0	1.0-1.1	0.575			
Co-morbidity						
0 (n=107)	1.0					
1 (n=139)	0.7	0.4-1.1	0.107			
2 or more (n=115)	0.7	0.4-1.2	0.251			
Histological type						
Adenocarcinoma (n=275)	1.0					
Squamous cell carcinoma (n=73)	1.4	0.8-2.3	0.222			
Other (n=13)	0.7	0.2-2.2	0.509			
Tumor location						
Mid (n=44)	1.2	0.6-2.4	0.537	1.5	0.7-3.1	0.260
Distal (n=238)	1.0			1.0		
GEJ (n=79)	1.6	0.9-2.6	0.082	1.0	0.6-1.8	0.964
Mean dose	1.0	1.0-1.0	0.987			
V20 per 10%*	1.0	1.0-1.0	0.701			
V25 per 10%*	1.0	1.0-1.1	0.615			
V30 per 10%*	1.0	1.0-1.1	0.628			
V35 per 10%*	1.0	0.9-1.1	0.775			
V40 per 10%*	1.0	0.9-1.1	0.580			
Mediastinal ratio#						
<0.5 (n=112)	1.0			1.0		
0.5-1.0 (n=218)	0.5	0.3-0.8	0.005	0.6	0.4-1.0	0.036
≥1.0 (n=28)	0.6	0.3-1.4	0.239	0.7	0.2-1.7	0.381
Type of surgery						
Transthoracic (n=84)	0.7	0.4- 1.3	0.248	0.7	0.4-1.3	0.243
Transhiatal (n=89)	1.5	0.8-2.6	0.182	1.3	0.7-2.4	0.419
Laparoscopic transhiatal (n=48)	1.9	0.9-3.7	0.076	1.7	0.8-3.5	0.163
Thoracoscopic/laparotomy (n=27)	0.9	0.4-2.2	0.855	0.9	0.4-2.2	0.829
Thoracoscopic/laparoscopic (n=113)	1.0			1.0		
Anastomotic leakage						
No (n=272)	1.0					
Yes (n=76)	1.4	0.9-2.4	0.162			
Unknown (n=13)	0.7	0.2-2.3	0.522			

* Odds ratios displayed in steps of 10%.

[#] Exclusion of 3 missings.

Table 4. Univariate and multivariate logistic regression analysis of a postoperative complicated course with a Clavien-Dindo classification of IIIB or higher (n=364).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age						
<70 (n=285)	1.0					
≥70 (n=79)	0.8	0.5-1.5	0.545			
Gender						
Male (n=290)	1.0					
Female (n=74)	1.5	0.9-2.6	0.129			
BMI	1.0	0.9-1.0	0.577			
Co-morbidity						
0 (n=108)	1.0			1.0		
1 (n=141)	1.3	0.7-2.4	0.367	1.3	0.7-2.5	0.353
2 or more (n=115)	2.1	1.2-3.9	0.013	2.4	1.3-4.5	0.006
Histological type						
Adenocarcinoma (n=276)	1.0			1.0		
Squamous cell carcinoma (n=75)	1.9	1.1-3.3	0.017	1.3	0.6-2.6	0.500
Other (n=13)	1.9	0.6-6.0	0.270	2.0	0.6-6.5	0.255
Tumor location						
Mid (n=46)	1.8	1.0-3.5	0.068	1.3	0.6-3.1	0.484
Distal (n=238)	1.0			1.0		
GEJ (n=80)	0.7	0.4-1.3	0.255	0.9	0.5-1.7	0.732
Mean dose	1.0	1.0-1.0	0.026	1.0	1.0-1.0	0.674
V20 per 10%	1.0	0.9-1.0	0.104			
V25 per 10%	0.9	0.9-1.0	0.115			
V30 per 10%	0.9	0.9-1.0	0.078	0.9	0.6-1.5	0.919
V35 per 10%	0.9	0.9-1.0	0.097	1.1	0.7-1.8	0.602
V40 per 10%	0.9	0.9-1.0	0.118			
Mediastinal ratio#						
<0.5 (n=114)	1.0			1.0		
0.5-1.0 (n=219)	2.0	1.2-3.5	0.012	1.9	1.0-3.5	0.036
≥1.0 (n=28)	3.3	1.4-8.1	0.008	2.2	0.8-6.1	0.143
Type of resection						
Transthoracic (n=86)	0.9	0.5-1.7	0.737			
Transhiatal (n=90)	0.8	0.6-1.6	0.592			
Laparoscopic transhiatal (n=48)	0.6	0.3-1.4	0.231			
Thoracoscopic/laparotomy (n=27)	1.4	0.6-3.3	0.486			
Thoracoscopic/laparoscopic (n=113)	1.0					

* Odds ratios displayed in steps of 10%.

Exclusion of 3 missings.

Discussion

In this study, the influence of the radiation dose to the future anastomotic region on the incidence of anastomotic complications and on the severity of these complications was determined in patients curatively treated for esophageal cancer. This study showed no significant influence of radiation dose to the future anastomotic region of the gastric fundus on the incidence of anastomotic leakage and stenosis with a radiation dose up to 41.4 Gy. However, an association was demonstrated between severe complications (≥ Clavien-Dindo IIIB) and the upper PTV border in relation to the mediastinal length, which implies that a higher mediastinal PTV border in combination with esophagectomy with gastric tube reconstruction and cervical anastomosis may increase the probability of severe complications.

An anastomotic leakage of 22% is comparable to rates in other studies with cervical anastomoses, including the prospective CROSS trial, in which a leakage rate of 26% was described[18]. The finding that the mean radiation dose and V20-V40 to the future anastomotic region of the gastric fundus were not correlated with anastomotic leakage is consistent with the results of our previous study with a smaller study population[8]. Furthermore, the CROSS trial patients receiving neoadjuvant chemoradiation had a non-significantly lower incidence of anastomotic leakage than the patients receiving esophagectomy alone (22% vs. 30%, respectively)[18]. A large series from a European multicenter study and two meta-analyses also demonstrated no significant difference in the anastomotic leakage rate between patients receiving neoadjuvant chemoradiation and surgery vs. surgery alone[9;10;19]. However, other studies have shown that the radiation dose to the gastric fundus was an independent predictor of anastomotic complications in patients undergoing intra-thoracic anastomosis[7]. This study included 54 patients with only 7 early anastomotic events. In contrast, a more recent study from the same group with a larger patient number did not reveal a dose-effect relationship with postoperative complications[20]. In our study we did not find a correlation between radiation dose to the gastric fundus and anastomotic complications with the use of 3-D conformal techniques. This is somewhat in contrast to a study of Wang et al.[21] who showed that a reduced dose to the normal tissues by using sophisticated techniques like Intensity-Modulated Radiotherapy (IMRT) or Proton Beam Therapy (PBT) reduced both pulmonary and gastro-intestinal complications compared to 3D Conformal Radiation Therapy (3D-CRT). An explanation for this different outcome might be the higher radiation dose that was used in their study (50.4Gy compared to 41.4Gy in current study) and a low median dose to the fundus in our study. Furthermore, a different chemotherapy scheme was used (cisplatinum/5-FU compared to carboplatin/paclitaxel in current study) which might have influenced the toxicity after neoadjuvant chemoradiation[22]. Our study revealed that squamous cell carcinoma was a significant predictor of anastomotic leakage. This finding is probably caused by the more proximal anatomical location of squamous cell tumors. This was also found in a large meta-analysis. A subgroup analysis of patients with a squamous cell carcinoma treated with neoadjuvant chemoradiation had a higher risk of postoperative mortality, treatment-related mortality and pulmonary complications compared to surgery alone. However, in patients with an adenocarcinoma there was no difference in mortality or postoperative complications[10].

A rate of anastomotic stenosis requiring dilatation(s) of 41% is consistent with a large study of patients undergoing esophagectomy with cervical anastomosis in which 42% of the patients developed a cervical stricture requiring dilatation(s)[23]. This study showed no influence of the mean radiation dose and V20-V40 on the development of anastomotic stenosis, which is consistent with two earlier studies[23;24]. However, the latter studies suggested that neoadjuvant chemoradiation appears to be associated with refractory strictures, requiring more than 10 dilations[23].

To date, the literature has reported conflicting results regarding whether neoadjuvant chemoradiation influences the severity of postoperative complications. A recent Swedish study also did not report an increase in postoperative complications by nCRT, but suggested a relationship between radiation dose to the future anastomotic site and the severity of postoperative complications[25]. In the current study, we observed an association with incidence of severe complications (≥ Clavien-Dindo IIIB) with the cranial PTV border in relation to the mediastinal length. This finding may imply that a higher mediastinal PTV border in combination with esophagectomy and cervical anastomosis increases the probability of severe complications. However, a proximal tumor location was a predictor of anastomotic leakage and not nCRT in a French study[19], and this result was also suggested by a meta-analysis[9] .Proximal tumor location is directly related to a more cranial extent of the PTV. Thus, whether the location of the superior PTV border or the proximal tumor location itself accounts for the increased severity remains unknown. Nevertheless, randomized studies comparing nCRT and esophagectomy with esophagectomy alone describe no differences in the overall incidence and severity of complications and morbidity between the two groups[18;19;26-28]. Furthermore, the suggested association between the superior border of the mediastinal PTV, as expressed as the mediastinal ratio, and the increased incidence of a complicated course with complications of a Clavien-Dindo score of ≥ IIIB should be interpreted with care, since the results were borderline significant and we did not observed an association between the mediastinal ratio and the incidence of anastomotic leakage. Since no significant differences in mortality between the two groups were observed, the fear for postoperative complications should be weighed against the 14% absolute 5 year overall survival advantage of neoadjuvant chemoradiation observed in the CROSS trial[29]. Irradiation to the remained cervical esophagus was unfortunately not registered in the database. This might be an important factor and should be addressed in further research in the future.

This study is limited by its retrospective nature; however, we included a large study population from two high-volume esophageal surgery centers in the Netherlands. The determination of the future anastomotic region after consultation of the surgeon may of course have a certain degree of inaccuracy. However, our method has been performed meticulously and is reproducible, in contrast with other studies. A minor statistical limitation in our study is the relative small group of patients with a mediastinal ratio of ≥1.0, however our chosen cut-off points are anatomically understandable and furthermore similar results were obtained when using the median of 0.6 as a cut-off point in the analysis.

In conclusion, this study demonstrates that with a mean radiation dose of 24.2 Gy to the future anastomotic region of the gastric fundus, the radiation dose was not associated with the incidence of anastomotic leakage or anastomotic stenosis in patients treated with nCRT followed by esophagectomy with gastric tube reconstruction with a cervical anastomosis. The incidence of severe complications was associated with the a high superior mediastinal PTV border without knowing whether the location of the superior PTV border or the proximal tumor location itself accounts for the increased severity. However, the possible increase in severe complications should be weighed against the potential survival benefit of a high upper mediastinal PTV border.

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PART III.

Summary and future perspectives

CHAPTER 10

Summary and future perspectives

Summary

In this thesis, patterns of care and the influence of neoadjuvant treatment on perioperative morbidity and oncological outcome in patients with esophageal cancer were investigated.

Part I. Patterns and determinants of care in patients with esophageal cancer

In the current literature most studies focus on results of patients treated in individual centres or on specific treatments strategies and not on the whole group of patients diagnosed with esophageal cancer. Therefore, the aim of **chapter two** was to determine, in a population-based setting, which factors influenced overall survival and whether these factors play a role in the decision to propose potentially curative treatment to patients with resectable esophageal cancer. Between 2003 and 2010, 849 patients with potentially resectable esophageal cancer were selected from the Eindhoven Cancer Registry. Forty-five percent of the patients underwent potentially curative surgery. Treatment modalities including surgery with or without neoadjuvant chemoradiation and definitive chemoradiation alone as well as the stage of disease were independent predictors of a better overall survival in patients with potentially resectable esophageal cancer. Although age and socioeconomic status had no significant influence on overall survival, a higher age and low socioeconomic status negatively influenced the probability to receive potentially curative treatment in patients with potentially resectable esophageal cancer.

Surgical treatment of esophageal cancer is a complex procedure with high postoperative morbidity, especially in elderly patients with multiple co-morbidities. This might be an argument to withhold these patients from surgical treatment and propose alternative strategies like definitive chemoradiation. Most treatment strategies and guidelines are based on clinical trials in which elderly patients are often excluded. Therefore, the aim of **chapter three** was to describe treatment patterns and its impact on overall survival in elderly patients (75 years and older) with potentially curable esophageal cancer in the Netherlands. Between 2003 and 2013, 4501 elderly patients with potentially curable esophageal cancer were selected from the nationwide population-based Netherlands Cancer registry. In this period, there was an increase in treatment with curative intent, with a consistent use of surgical treatment with or without neoadjuvant treatment and a significant increase in the use of definitive chemoradiation among elderly patients. The increase in administration of definitive chemoradiation was most prominent in elderly patients with a squamous cell carcinoma. Multivariable Cox regression analysis showed no difference in overall survival between patients who received surgery with neoadjuvant chemo(radio) therapy, surgery alone or definitive chemoradiation among elderly patients with a squamous cell carcinoma. However, elderly patients with an adenocarcinoma that underwent surgery with neoadjuvant chemo(radio)therapy had a better overall survival compared to patients who underwent surgery alone or definitive chemoradiation.

Due to a process of centralization, treatment of esophageal cancer in the Netherlands is now largely performed in regional referral centres. In these centres, patients are discussed at multidisciplinary team (MDT) meetings and managed according to the national guidelines and latest evidence. Concentration of esophageal cancer care is associated with improved overall survival. However, most patients with esophageal cancer are diagnosed in non-referral centres and might not be discussed within MDT meetings with proficient knowledge of all aspects of diagnosis and treatment of esophageal cancer. In these hospitals of diagnosis however, the decision is made whether or not a patient is referred to an expert centre for further treatment. The aim of both **chapter four and chapter five** was to assess the relationship between hospital of diagnosis and referral for a curative treatment. Secondly, the referral pattern and its influence on overall survival in patients with resectable esophageal cancer was explored. In **chapter four**, 849 patients with potentially resectable esophageal cancer were selected from the Eindhoven Cancer registry between 2003 and 2010. In this registry, co-morbidity has been registered systematically and therefore multivariate regression analysis could be performed which included adjustments for co-morbidity. A difference in the proportion of patients referred for surgery was observed, ranging from 33% to 67% between hospitals of diagnosis. Furthermore, a large variation between the referring hospitals was observed in patients that underwent definitive chemoradiation (8% to 25%). Patients diagnosed in the majority of hospitals were less likely to receive treatment with a curative intent (surgery or definitive chemoradiation) compared to being diagnosed in the reference centre with the highest probability to receive this treatment. Furthermore, multivariable survival analysis showed that hospital of diagnosis also affected overall survival. In **chapter five**, these results could be confirmed on a nationwide level. Patients with potentially curable esophageal cancer (n=13017) diagnosed in 91 hospitals between 2005 and 2013, were selected from the nationwide Netherlands cancer registry. The proportion of patients receiving curative treatment ranged from 37% to 83% and from 45% to 86% in the periods 2005-2009 and 2010-2013, respectively, depending on hospital of diagnosis. After adjustment for patient- and hospital-related characteristics these proportions ranged from 41% to 77% and from 50% to 82%, respectively. Multivariable survival analyses showed that patients diagnosed in hospitals with a low probability of undergoing curative treatment had a worse overall survival compared to those diagnosed in hospitals with a high probability. These two studies revealed a large variation in the probability to undergo curative treatment for esophageal cancer depending on the hospitals of diagnosis, which also affected the survival of these patients. Regional expert MDT meetings with involvement of experienced specialists in this field should thus be initiated for all patients with esophageal cancer. The decisions made by these expert panels may improve the selection of patients with esophageal cancer who are eligible for a curative treatment option leading to an overall improvement of survival on the long term.

Part II. The influence of neoadjuvant treatment on morbidity and oncological outcome in esophageal surgery

In the literature there is no conclusive evidence which perioperative regime (chemotherapy or chemoradiation) and which surgical resection (esophagectomy or gastrectomy) should be used in treatment of GEJ tumors since there are no specific trials performed in GEJ tumors and the two cornerstone perioperative trials (MAGIC and CROSS) both included GEJ tumors. Therefore, **chapter six** evaluates in a population-based setting, the patterns of care in treatment strategies for patients with resectable adenocarcinomas of the GEJ and to compare oncological outcomes. From the nationwide population-based Netherlands Cancer Registry 1196 patients with potentially resectable GEJ tumors diagnosed between 2005 and 2012 who received surgical treatment were selected. Seventy-nine percent of the patients received an esophagectomy and 21% were treated with a gastrectomy. Similar oncological outcomes were noted between the two types of resection with respect to lymph node yield, lymph node ratio and radicality. No survival difference was observed between patients treated with an esophagectomy or a gastrectomy regardless of neoadjuvant treatment. However, perioperative chemotherapy or neoadjuvant chemoradiation were strongly correlated with oncological outcome. Therefore, any perioperative treatment with chemotherapy or chemoradiation rather than the surgical approach appeared to be most critical factor for overall survival.

Surgery after completion of neoadjuvant chemoradiation is routinely performed within 2 to 8 weeks following guidelines based on randomised controlled trials. In practice however, surgery is often postponed due to several factors like toxicity of neoadjuvant chemoradiation, comorbidity, poor physical status or logistical problems. It is unclear whether or not postponing surgery after completion of neoadjuvant chemoradiation influences postoperative outcomes. Therefore, **chapter seven** evaluates the influence of the time period between neoadjuvant chemoradiation and surgery on the postoperative course, pathological response, and long-term survival in patients with esophageal adenocarcinoma. Between 2001 and 2014, 190 patients with esophageal adenocarcinoma were treated with neoadjuvant chemoradiation followed by esophagectomy. Of these patients 125 received surgery more than 8 weeks after completion of neoadjuvant chemoradiation. Multivariable analysis revealed that time to surgery did not significantly influence postoperative morbidity, pathologic complete response rates and five-year overall survival. These results suggest that it is safe to postpone surgery beyond 8 weeks if needed. On the other hand, postponing surgery beyond 8 weeks does also not have any additional advantages.

The preferred treatment for non-metastatic esophageal cancer in the Netherlands is neoadjuvant chemoradiation followed by a transhiatal or transthoracic esophagectomy. Esophageal surgery has high postoperative morbidity rates and anastomotic complications such as leakage and stenosis. Neoadjuvant chemoradiation might be a factor influencing postoperative anastomotic complications. Therefore, the aim of **chapter eight and nine** was to determine the influence of radiation dose to the fundus of the stomach on the development of anastomotic complications in patients treated with neoadjuvant chemoradiation followed by esophagectomy. **In chapter eight**, data were used from 53 patients with esophageal cancer in the Catharina Hospital Eindhoven who received neoadjuvant chemoradiation (41.4Gy combined with chemotherapy) followed by transhiatal esophagectomy with cervical anastomosis between 2009 and 2011. On planning CT, radiation dose on the future anastomotic region of the gastric fundus was determined. Anastomotic leakage occurred in 26% of the patients and anastomotic stenosis in 45%. Multivariable analysis revealed no influence of the radiation dose on the future anastomotic region on anastomotic leakage and stenosis.

In chapter nine, 364 consecutive patients with esophageal cancer, diagnosed in two high-volume esophageal surgery centers (i.e. Catharina Hospital Eindhoven and the Academic Medical Centre Amsterdam), treated with neoadjuvant chemoradiation (41.4 Gy combined with chemotherapy) followed by an esophagectomy and cervical anastomosis were included. The future anastomotic region in the gastric fundus was determined and the mean dose and upper planning target volume (PTV) border in relation to mediastinal length expressed as the mediastinal ratio were calculated. Anastomotic leakage occurred in 22% and anastomotic stenosis in 41%. Mean dose of 24.2 Gy to the future anastomotic region of the gastric fundus were not associated with the incidence of anastomotic leakage or anastomotic stenosis. In 28% of the patients, severe complications (Clavien-Dindo score of ≥ IIIB) occurred. An association was demonstrated between severe complications (≥ Clavien-Dindo IIIB) and the upper PTV border in relation to the mediastinal length, which implies that a higher mediastinal PTV border in combination with esophagectomy with gastric tube reconstruction and cervical anastomosis may increase the probability of severe complications. However, the possible increase in severe complications should be weighed against the potential survival benefit of a high upper mediastinal PTV border.

Future perspectives

In the first part of this thesis patterns of care and treatment decisions are investigated in a population based setting. Since it represents the total patient population it provides an overview of everyday clinical practice. However, the translation to the individual patient in clinical setting is always a challenge. Determinants in decision making and patterns of care are of crucial importance especially by the introduction of concentration of care. This concentration of care has proven its effectiveness in terms of postoperative morbidity and a more tailored-made decision making in a multidisciplinary approach. However, it has also led to a new phenomenon, which is the importance of the hospital of diagnosis in this process, since this is the first chain in the decision making process. Furthermore, concentration of care could potentially lead to a decrease in treatment decisional capacities of the teams in the less experienced hospitals of diagnosis. Hence, concentration of care could potentially lead to an unwanted “brain drain” of specific knowledge out of the hospitals of diagnosis. Therefore, we believe that regional tumor specific video MDT’s with treating physicians as well as tumor specific experts should be implemented. The initiative to organize these regional MDT’s should be coordinated by the expert centre. The Netherlands Comprehensive Cancer organization and regional Comprehensive Cancer Networks could coordinate this process on a national and regional level and the government and insurance companies could provide the technical infrastructure.

As described in chapter four and five, hospital of diagnosis plays an important role in esophageal cancer treatment. Concentration of esophageal cancer is one of many cancer types which are concentrated in high volume centres in the Netherlands. Therefore, further research on the influence of hospital of diagnosis on other centralised cancer types such as gastric, pancreatic and hepatobilliary cancer should be performed in the near future.

A limitation in this thesis is that we focussed on resectable esophageal cancer patients only. Unfortunately, most patients are treated in a palliative setting. Since there are many different options in palliative and supportive care it is important to discuss all patients in MDT meetings diagnosed with esophageal cancer. Furthermore, research should also focus on palliative and non surgical treatment decisions.

In this thesis we also focussed on the growing group of elderly patients. The overall western population is ageing and therefore the elderly patients constitute a large and increasing part of the overall population. However, elderly patients are very often excluded from randomised controlled trials. In this thesis we described patterns of care in the elderly patients and revealed no survival difference in elderly patients with squamous cell carcinoma receiving surgery or definitive chemoradiation.

Therefore, definitive chemoradiation appears to be a good alternative to surgery in elderly patients with squamous cell carcinoma, though in elderly patients with an adenocarcinoma surgery leads to a better overall survival compared to definitive chemoradiation. However, this survival advantage after surgery should be weighed against the postoperative morbidity and decrease in health-related quality of life. Since a randomised trial in only the elderly patients will be very difficult these results however advocate for inclusion of elderly in clinical trials. Furthermore, this is a warm plea for the SANO trial which will randomize direct surgery after neoadjuvant CRT and a watchful follow up strategy with only surgery when needed in case of recurrence of residual disease.

In the literature there is an ongoing discussion on the optimal surgical treatment (esophagectomy or gastrectomy) and perioperative treatment (chemoradiation or chemotherapy) in patients with a resectable GEJ tumor. In this thesis we revealed in a population based setting that there was no survival difference between esophagectomy or gastrectomy, however perioperative chemotherapy and neoadjuvant chemoradiation were strongly correlated with oncological outcome. The surgical decision making for optimal treatment is mainly based on tumor ingrowth into the esophagus and surgeons' preference. Since we could not observe a difference in outcome regarding the surgical strategy, we should focus on the optimal perioperative treatment. In order to achieve conclusive evidence on optimal perioperative treatment, a randomised controlled trial is needed which will compare neoadjuvant chemoradiation and perioperative chemotherapy followed by surgery. Fortunately, an Irish trial is currently recruiting patients with esophageal and GEJ tumors to compare the MAGIC regimen with the CROSS regimen. This study might provide more insight into the optimal preoperative strategy.

Since the introduction of neoadjuvant chemoradiation there is discussion on the timing of subsequent surgery after neoadjuvant treatment and also on the influence of neoadjuvant chemoradiation on postoperative morbidity. Timing of surgery after neoadjuvant chemoradiation is a difficult subject to investigate since it is depending on many factors such as toxicity of neoadjuvant treatment, comorbidity, patient's physical status and also logistical problems. Furthermore, also tumor characteristics like histology and classification play a role. A large population based study in which for all those confounding factors can be adjusted probably will lead the way in providing an optimal treatment timeframe. In addition, new biological tumor characteristics will be developed in order to further personalize the choice and timing of optimal treatment strategy.

Furthermore, another very interesting patient group are those that have a pathologically complete response after neoadjuvant chemoradiation. Especially in the patients with a squamous cell carcinoma the complete response rate after neoadjuvant chemoradiation was 49% in the CROSS trial. It will be important to determine a safe and reliable surveillance in patients with a complete response which might eventually lead to a wait and see policy with only performing surgery when needed as will be investigated in the SANO trial.

In this thesis we investigated the influence of radiation dose to the gastric fundus and their influence of anastomotic complications. In both of our studies we found no relation between radiation dose and anastomotic complications. Therefore, we believe that the negative effects of radiation on postoperative anastomotic complications are overestimated in the current literature. Other factors like the surgical approach comparing intrathoracic anastomosis versus cervical anastomosis might be of more importance. Besides that, we should not underestimate the important survival benefit of neoadjuvant radiation therapy. We do believe however that further research on radiation dose to the part of the esophagus which is used for the anastomosis is necessary. Therefore, we advocate for new research which determines influence of radiation on complications after Ivor-Lewis esophagectomy with an intrathoracic anastomosis.

In conclusion, every patient, independent of the hospital of diagnosis, deserves the optimal curative or palliative management in which factors like quality of life, age, fragility, neoadjuvant treatment and the probability of complications on oncological and surgical outcome are taken into account. Every patient should be discussed in obligatory tumor specific multidisciplinary board meetings. This can be achieved by a regional network of open access tumor specific video multidisciplinary board meetings which are organized by regional expert centres. This will reduce variation in care and will provide optimal patient tailored management.

Nederlandse samenvatting

In dit proefschrift worden verschillende patronen van zorg en de invloed van neoadjuvante behandeling op morbiditeit en oncologische uitkomst onderzocht bij patiënten met een slokdarmcarcinoom.

Deel I Besluitvorming in behandeling van het slokdarmcarcinoom.

In de beschikbare wetenschappelijke literatuur wordt er met name aandacht besteed aan resultaten van behandelingen in een bepaald ziekenhuis. In deze literatuur wordt niet zozeer gekeken naar de gehele groep patiënten met een slokdarmcarcinoom in een populatie. Daarom was het doel van **hoofdstuk twee** om in een populatie onderzoek factoren te bepalen die van invloed zouden kunnen zijn op de overleving van patiënten met een slokdarmcarcinoom. Tevens was het doel om te onderzoeken of deze factoren een rol spelen in de besluitvorming voor het al dan niet krijgen van een curatieve behandeling. Tussen 2003 en 2010 werden 849 patiënten met een resectabel slokdarmcarcinoom geselecteerd uit de Eindhoven Kanker Registratie. Vijfenveertig procent van de patiënten kreeg een chirurgische behandeling. Behandelingen, zoals chirurgie en chemoradiatie, en tevens tumorstadium waren onafhankelijke voorspellers voor een betere overleving bij patiënten met een slokdarmcarcinoom. Hoewel leeftijd en sociaaleconomische status geen significante invloed hadden op de overleving, waren een hogere leeftijd en een lage sociaaleconomische status factoren die invloed hadden op het al dan niet krijgen van een curatieve behandeling bij patiënten met een resectabel slokdarmcarcinoom.

Chirurgische behandeling van het slokdarmcarcinoom is een complexe behandeling waarbij vaak postoperatieve morbiditeit optreedt, met name bij patiënten op leeftijd met veel comorbiditeit. Dit zou een argument kunnen zijn om deze patiëntengroep een alternatief voor een chirurgische behandeling te bieden. De meeste behandelstrategieën en richtlijnen zijn echter gebaseerd op klinische studies waarbij patiënten op leeftijd vaak zijn uitgesloten van deelname. Het doel van **hoofdstuk drie** was daarom om de verschillende patronen in de geleverde zorg te beschrijven en tevens te onderzoeken welke invloed dit heeft op de overleving bij oudere patiënten (75+) met een, in principe, curatief te behandelen slokdarmcarcinoom in Nederland. Tussen 2003 en 2013 werden 4501 oudere patiënten met een dergelijk curatief te behandelen slokdarmcarcinoom geselecteerd uit een nationale database van de Nederlandse Kanker Registratie. Tussen 2003 en 2013 was er een toename in curatieve behandeling, waarbij het aandeel chirurgische behandeling al dan niet in combinatie met neoadjuvante therapie gelijk bleef, maar er een significante toename was in de toepassing van definitieve chemoradiatie bij de oudere patiëntengroep. Deze toename van definitieve chemoradiatie was met name te zien bij oudere patiënten met een plaveiselcel carcinoom. Multivariabele analyse liet zien dat er geen verschil was in overleving bij oudere patiënten met een plaveiselcel carcinoom die werden behandeld met neoadjuvante chemo(radio)therapie gevolgd door chirurgie danwel met definitieve chemoradiatie. Echter, bij oudere patiënten met een adenocarcinoom was de overleving na neoadjuvante chemo(radio)therapie gevolgd door chirurgie significant beter dan na alleen chirurgie of definitieve chemoradiatie.

Door de centralisatie van zorg in Nederland wordt de behandeling van het slokdarmcarcinoom nu met name uitgevoerd in regionale verwijscentra. In deze verwijscentra worden de patiënten besproken in multidisciplinaire teams en behandeld volgens de nationale richtlijnen en recente wetenschappelijk literatuur. Concentratie van zorg bij het slokdarmcarcinoom heeft geleid tot een verbetering in overleving. Echter, de meeste patiënten met een slokdarmcarcinoom worden in Nederland niet gediagnosticeerd in een expertise centrum maar in een verwijzend ziekenhuis waar wellicht niet alle expertise op het gebied van slokdarmkanker aanwezig is. De beslissing om een patiënt al dan niet door te verwijzen naar een expertise centrum voor verdere behandeling wordt gemaakt in het ziekenhuis van diagnose. Derhalve was het doel van **hoofdstuk vier en hoofdstuk vijf** om bij patiënten met een resectabel slokdarmcarcinoom de relatie tussen het ziekenhuis van diagnose en de kans op een curatieve behandeling te onderzoeken. Daarnaast werd deze kans op een curatieve behandeling gerelateerd aan de kans op overleving. Voor **hoofdstuk vier** werden 849 patiënten met een potentieel resectabel slokdarmcarcinoom in de periode 2003 tot 2010 geselecteerd uit de Eindhoven Kanker Registratie. In deze registratie wordt comorbiditeit systematisch geregistreerd waardoor het mogelijk is om een multivariabele regressie analyse toe te passen waarbij wordt gecorrigeerd voor comorbiditeit. Het percentage patiënten dat een chirurgische resectie onderging varieerde tussen de 33 en 67%. Tevens werd er een grote variatie gezien tussen de verwijzende ziekenhuizen met betrekking tot de kans op het krijgen van definitieve chemoradiatie (8% tot 25%). De patiënten gediagnosticeerd in een meerderheid van de ziekenhuizen hadden minder kans op het krijgen van een in opzet curatieve behandeling (chirurgie of definitieve chemoradiatie) dan patiënten die werden gediagnosticeerd in het verwijscentrum met de hoogste kans op een curatieve behandeling. Daarnaast liet de multivariabele overlevingsanalyse zien dat ziekenhuis van diagnose een duidelijk effect had op de overleving. Voor **hoofdstuk vijf** werd een landelijke studie verricht en werden 13017 patiënten met een potentieel resectabel slokdarmcarcinoom, gediagnosticeerd in 91 ziekenhuizen tussen 2005 en 2013, geselecteerd uit de nationale Nederlandse Kanker Registratie. Afhankelijk van het ziekenhuis van diagnose, bleek het aantal patiënten dat een behandeling met een curatieve intentie kreeg te variëren van 37% tot 83% en van 45% tot 86% in respectievelijk de perioden 2005-2009 en 2010-2013. Multivariabele overlevingsanalyse liet zien dat patiënten gediagnosticeerd in ziekenhuizen met een lage kans op het ondergaan van een in opzet curatieve behandeling een slechtere overleving hadden dan patiënten welke werden gediagnosticeerd in een ziekenhuis met een hoge kans op het krijgen van een dergelijke curatieve behandeling. Beide studies lieten, afhankelijk van het ziekenhuis van diagnose, een grote variatie zien in de kans op het krijgen van een in opzet curatieve behandeling bij het slokdarmcarcinoom, welke tevens de overlevingskansen van deze patiënten beïnvloedde. Regionaal multidisciplinair (video-)overleg met betrokkenheid van slokdarmkanker experts zou een oplossing kunnen zijn voor alle patiënten gediagnosticeerd met een slokdarmcarcinoom. Dergelijke besluitvorming zou kunnen zorgen voor een betere selectie van patiënten die in aanmerking komen voor een curatieve behandeling welke zal leiden tot een verbetering in overleving op de lange termijn.

Deel II De invloed van neoadjuvante behandeling op morbiditeit en oncologische uitkomst na slokdarmchirurgie

Patiënten, gediagnosticeerd met een slokdarm/maag overgangstumor (cardiacarcinoom), worden behandeld door middel van een slokdarmresectie gevolgd door een buismaagreconstructie of door een (totale) maagresectie met oesophagojejunostomie. De beschikbare wetenschappelijke literatuur geeft nog geen sluitend bewijs over de beste behandeling voor patiënten met een cardiacarcinoom. In **hoofdstuk zes** werd - door middel van een populatie onderzoek - de zorgpatronen en behandelstrategieën bij patiënten met een resectabel adenocarcinoom van de cardia onderzocht, en werden oncologische uitkomsten vergeleken. Voor dit onderzoek werden uit de Nederlandse Kanker Registratie 1196 patiënten geselecteerd met een in potentie resectabel cardiacarcinoom (gediagnosticeerd tussen 2005 en 2012) die werden behandeld met een chirurgische resectie. Negenenzeventig procent van de patiënten werd behandeld met een slokdarmresectie en 21% met een maagresectie. Tussen deze twee behandelingen werden gelijkwaardige chirurgische uitkomsten gezien wat betreft lymfeklieropbrengst, lymfeklier ratio and radicaliteit. Daarnaast werd er onafhankelijk van neoadjuvante behandeling geen verschil in overleving gezien tussen patiënten die werden behandeld met een slokdarmresectie danwel een maagresectie. Echter de perioperatieve chemotherapie en de neoadjuvante chemoradiatie waren beiden bepalend voor de oncologische uitkomst. Daaruit is gebleken dat perioperatieve behandeling met chemotherapie dan wel chemoradiatie een belangrijkere rol speelde in de overleving dan de chirurgische benadering.

Een chirurgische resectie wordt routinematig uitgevoerd 2 tot 8 weken nadat de neoadjuvante chemoradiatie is afgerond, gebaseerd op richtlijnen al dan niet uit gerandomiseerd onderzoek. Echter in de praktijk wordt de chirurgische resectie vaak uitgesteld door verschillende factoren, zoals toxiciteit na neoadjuvante chemoradiatie, comorbiditeit, slechte fysieke gesteldheid of door logistieke problemen. Het is onduidelijk of de lengte van de wachttijd tussen operatie en neoadjuvante behandeling invloed heeft op de postoperatieve uitkomst. In **hoofdstuk zeven** werd geëvalueerd of de wachttijd tussen de neoadjuvante chemoradiatie en de chirurgische resectie invloed heeft op het postoperatieve beloop, de pathologische respons en overleving op de lange termijn bij patiënten met een adenocarcinoom van de slokdarm. Tussen 2001 en 2014 werden 190 patiënten met een adenocarcinoom van de slokdarm behandeld met neoadjuvante chemoradiatie gevolgd door een slokdarmresectie. Bij 125 patiënten was de wachttijd tussen neoadjuvante behandeling en de chirurgische resectie meer dan 8 weken. Multivariabele analyse liet zien dat het tijdsinterval tot chirurgie geen significante invloed had op de postoperatieve morbiditeit, pathologische respons and 5-jaarsoverleving. Deze resultaten toonden aan dat - indien nodig - het veilig is om de chirurgische resectie meer dan 8 weken na het afronden van neoadjuvante chemoradiatie te verrichten. Echter het liet ook zien dat het uitstellen van de chirurgische resectie geen extra voordelen geeft.

Bij de behandeling van patiënten in Nederland met een niet uitgezaaid slokdarmcarcinoom heeft neoadjuvante chemoradiatie gevolgd door transhiatale of transthoracale slokdarmresectie de voorkeur. Een slokdarm operatie heeft een hoge postoperatieve morbiditeit en tevens complicaties gerelateerd aan de anastomose zoals lekkage en stenose. Neoadjuvante chemoradiatie zou een rol kunnen spelen in het ontstaan van deze postoperatieve anastomose complicaties. Het doel van **hoofdstuk acht en negen** was derhalve om de invloed van dosis van de bestraling op de fundus van de maag op het ontstaan van anastomose gerelateerde complicaties te onderzoeken. Voor **hoofdstuk acht** werden 53 patiënten opgenomen in het onderzoek met een slokdarmcarcinoom die tussen 2009 en 2011 in het Catharina Ziekenhuis werden behandeld met neoadjuvante chemoradiatie (41.4 Gy gecombineerd met chemotherapie), gevolgd door een transhiatale slokdarmresectie met een cervicale anastomose. Op de planning CT, werd de radiatie dosis op de fundus van de maag - waar de toekomstige anastomose mee zou worden gemaakt - bepaald. Bij 25.5% van de patiënten ontstond een naadlekkage en bij 45.3% een naadstenose. Multivariabele analyse liet echter geen invloed van radiatie dosis zien op het ontstaan van naadlekkage en stenose. Voor **hoofdstuk negen** werden 364 patiënten met een slokdarmcarcinoom die zijn behandeld met neoadjuvante chemoradiatie (41.4Gy gecombineerd met chemotherapie) gevolgd door een slokdarmresectie met een cervicale naad in het onderzoek opgenomen. Deze patiënten zijn gediagnosticeerd in twee hoogvolume ziekenhuizen (het Catharina Ziekenhuis Eindhoven en het Academisch Medisch Centrum Amsterdam). De toekomstige anastomose regio van de maag fundus werd bepaald en daarnaast werd de gemiddelde dosis, en de bovengrens mediastinale planning target volume (PTV) in relatie tot de mediastinale lengte uitgedrukt als mediastinaal ratio berekend. In deze groep ontstond bij 22% van de patiënten een naadlekkage en bij 41% een naadstenose. Een gemiddelde dosis van 24.2 Gy op de toekomstige anastomose regio had ook in deze grotere en multi-institutionele studie geen invloed op de incidentie van naadlekkage of stenose. Bij 28% van de patiënten ontwikkelde zich een ernstige complicatie (Clavien Dindo 3B of hoger). Er werd wel een relatie gezien tussen het ontstaan van ernstige complicaties en de mediastinale PTV bovengrens in relatie met de mediastinale lengte. De geconstateerde relatie suggereerde dat een hogere mediastinale PTV bovengrens bij patiënten na slokdarmresectie met buismaagreconstructie en cervicale anastomose en hogere kans hadden op het ontwikkelen van ernstige postoperatieve complicaties. Deze mogelijk hogere kans op ernstige complicaties moet worden afgezet tegen de potentiële overlevingswinst van een hogere mediastinale PTV bovengrens.

Curriculum Vitae

Marijn Koëter werd op 8 november 1987 in Eindhoven geboren. Hij groeide op in Son en Breugel samen met zijn ouders en twee jongere broers. Na zijn basisschool in Son en Breugel te hebben voltooid, ging hij naar het VWO op het Stedelijk College te Eindhoven. Hier behaalde Marijn zijn VWO diploma, om vervolgens zijn weg te vervolgen naar Maastricht. Daar begon hij op de universiteit aan de studie geneeskunde. In het laatste jaar deed hij zijn wetenschappelijke stage en tevens zijn laatste keuze co-assistentschap chirurgie in het Catharina Ziekenhuis Eindhoven onder begeleiding van dr. G.A.P Nieuwenhuijzen en prof. dr. V.E.P.P Lemmens. Daar werd het begin gemaakt aan dit promotieonderzoek. Nadat Marijn zijn arts diploma behaalde in 2012 heeft hij als arts-assistent (niet in opleiding) gewerkt op de afdeling chirurgie van het Catharina Ziekenhuis Eindhoven, het Elkerliek Ziekenhuis te Helmond en in het Máxima Medisch Centrum te Veldhoven. Tijdens zijn werkzaamheden in de kliniek continueerde hij zijn wetenschappelijke onderzoek in samenwerking met het Integraal Kanker Centrum Nederland en het Catharina Ziekenhuis Eindhoven, welke uiteindelijk hebben geleid tot dit promotieonderzoek. In juli 2015 is Marijn gestart als chirurg in opleiding in het Maastricht Universitair Medisch Centrum, waarna hij in mei 2017 terugkeerde in het Catharina Ziekenhuis Eindhoven voor de laatste vier jaar van zijn opleiding tot chirurg. In zijn vrije tijd is Marijn een fanatieke voetballer bij het eerste elftal van SBC en daarnaast tennist hij regelmatig. Marijn is al vele jaren samen met Lisanne de Wit en woont met haar samen in Son en Breugel.

PhD Portfolio

Name PhD student:	Marijn Koëter
Erasmus MC department:	Public Health
PhD period:	July 2012 - June 2017
Promotores:	V.E.P.P. Lemmens and H.J.T. Rutten
Co-promotores:	G.A.P. Nieuwenhuijzen and R.H. Verhoeven

Work experience

2012-2015	Surgical resident (not in training) at Catharina Hospital Eindhoven, Elkerliek Hospital Helmond and Máxima Medical Centre Veldhoven
2015-2017	Surgical resident (in training) at Maastricht University Medical Centre
2017-present	Surgical resident (in training) at Catharina Hospital Eindhoven

Presentations

ESSO 2012	Higgins Award Sessions (second prize winner); Hospital of diagnosis plays a role in offering potential curative treatment to patients with resectable esophageal cancer in the Netherlands: A population based study
ESSO 2012	Long term follow-up of a novel regimen of neoadjuvant paclitaxel, carboplatin, 5-FU and radiation therapy followed by surgery shows a very high response rate and the importance of radical surgery
ESSO 2012	Determinants in decision making for curative surgery and survival in patients with resectable esophageal cancer in the Netherlands: a population-based study
NVGE Congress 2013	The role of hospital of diagnosis in offering curative surgery and the impact on survival in resectable oesophageal cancer
Chirurgendagen 2013	The role of hospital of diagnosis in offering curative surgery and the impact on survival in resectable oesophageal cancer
ESSO 2014	The influence of the region and type of hospital of diagnosis on the probability to receive curative treatment for resectable esophageal cancer in the Netherlands

ESSO 2014	Not the type of surgical treatment but neoadjuvant treatment influences overall survival in patients with gastro-esophageal junction tumours in the Netherlands
DUCG 2015	De invloed van bestralingsdosis op het ontstaan postoperatieve complicaties na slokdarmchirurgie
NVGE 2015	Patterns of care and overall survival in elderly patients with resectable esophageal cancer in the Netherlands: a population-based study

Poster presentations

ECCO 2013	Radiation dose does not influence anastomotic complications in patients with oesophageal cancer treated with neoadjuvant chemoradiation and transhiatal oesophagectomy
ESDE 2014	Not the type of surgical treatment but neoadjuvant treatment influences overall survival in patients with gastro-esophageal junction tumors in the Netherlands
ESDE 2014	The influence of delaying surgery for esophageal adenocarcinoma after neoadjuvant chemoradiation on postoperative outcome
ESDE 2016	Influence of the extent and dose of radiation on complications after neoadjuvant chemoradiation and subsequent esophagectomy with gastric tube reconstruction with a cervical anastomosis

Membership

2015 - present	Nederlandse Vereniging voor Heelkunde
2017 - present	De Jonge Specialist

List of publications

This thesis

M. Koëter, L.N. van Steenbergen, V.E. Lemmens, H.J.T. Rutten, J.A. Roukema, G.A.P. Nieuwenhuijzen. *Determinants in decision making for curative surgery and survival in patients with resectable oesophageal cancer in the Netherlands: a population-based study.* Cancer Epidemiology 39 (2015) 863–869.

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Other

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