Adenocarcinoma of the gastroesophageal junction: challenges in staging and treatment

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PhD thesis, Utrecht University, The Netherlands

Publication of this thesis was financially supported by Nederlandse Vereniging voor Gastroenterologie and Chipsoft.

Cover	Adriaan de Wolf
Lay-out & cover editing	Sander Treur
Printed by	Gildeprint
ISBN	978-94-6233-512-7

Adenocarcinoma of the gastroesophageal junction: challenges in staging and treatment

Adenocarcinoom van de gastro-oesofageale overgang:
uitdagingen in diagnostiek en behandeling
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 2 februari 2017 des middags te 4.15 uur

door

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geboren op 7 augustus 1988
te Alkmaar

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GENERAL INTRODUCTION AND THESIS OUTLINE

Adenocarcinoma of the gastroesophageal junction

Over the past 50 years there has been a remarkable change in the epidemiology of esophageal cancer. Once a rare tumor, adenocarcinoma of the esophagus and gastroesophageal junction (GEJ) has seen a rapid increase in incidence over the last decades. It is now the most common esophageal cancer in western countries[1, 2]. In the Netherlands, a threefold increase was seen for esophageal cancer, mainly due to the rise in adenocarcinoma of the GEJ[3]. The specific etiological factors that contribute to the occurrence of cancer at the GEJ are insufficiently elucidated. Many potential risk factors have been evaluated, sometimes with conflicting results. One factor that is the increased exposure of the esophagus to gastric and intestinal reflux juice, which could lead to intestinal metaplasia, or Barrett's. This is considered to be a major risk factor for cancer[4].

Adenocarcinomas of the GEJ are located at the transitional area of the esophagus and stomach. However, the relationship between adenocarcinoma of the esophagus and the cardia still remains controversial. Distal esophageal tumors may grow downward past the anatomical GEJ and involve the cardia. Vice versa, tumors that arise from the cardia often extend proximal into the distal esophagus. Hence, there is considerable overlap and therefore it is difficult to assign a given tumor to be either from esophageal or gastric origin. In an attempt to help assigning these tumors to their origin, Siewert and colleagues developed a classification system to categorize these tumors in to three different types according to their anatomic and topographic location[5]. Type I arises from 5 to 1 cm proximal from the anatomic GEJ and is classified as an adenocarcinoma of the distal esophagus. Type II arises from 1cm proximal to 2cm distal from the GEJ and is labeled as a true cardiacarcinoma. Type III arises from 2 to 5cm distal from the GEJ and is generally called subcardial gastric carcinoma (Figure 1).

Diagnostic work-up

Staging of GEJ tumors is performed according to the 7th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) for both esophageal and gastric cancer[6]. Adenocarcinomas of the GEJ are staged according to the esophageal scheme if the tumor extends into the distal esophagus. In case the tumor does not extend into the esophagus, these tumors are staged as gastric tumors. However, the esophageal and gastric scheme differ quite substantially. In the gastric scheme a T4a tumor invades the serosa of the stomach whereas in the esophageal scheme these tumors invade in adjacent structures such as pleura, pericardium or diaphragm. This makes it difficult to compare the effect of treatment between studies since some studies will use the gastric scheme and some the esophageal scheme for true cardiacarcinomas. It would be recommended to classify all GEJ tumors the same to compare studies more accurately.

Several diagnostics modalities are used for determining the exact tumor localization and TNM staging. The diagnosis of GEJ cancer is made or confirmed with upper endoscopy and biopsy. Upper endoscopy can also provide important information on the localization and stage of the tumor. Pretreatment TNM staging is typically performed with a combination of endoscopic ultrasound (EUS) and thoraco-abdominal computed tomography (CT). For the detection of distant metastasis 18F-fluorodeoxyglucose positron emission tomography (18-FDG PET) is gaining popularity as standard modality. There are, however, several studies that have reported that the current diagnostic modalities have their limitations in accurately determining tumor location, infiltration depth and the presence of metastatic lymph nodes[7-9]. Since the choice of treatment of GEJ tumors largely depends on diagnostic findings, accurate diagnostic staging is important to elaborate an individualized treatment strategy.

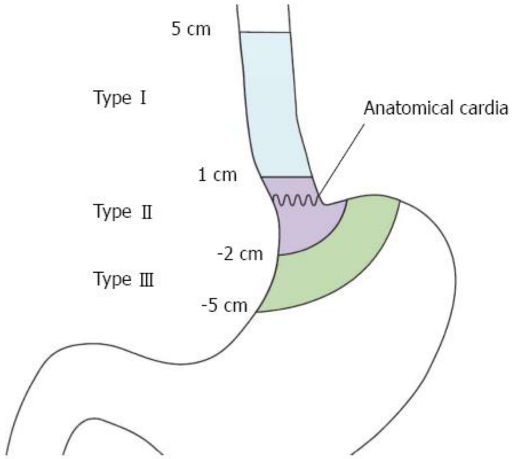

Figure 1 Siewert classification

Treatment strategies

Historically, GEJ adenocarcinomas were treated with surgery alone. However, survival rates have improved due to the increased use of multimodality treatment protocols in recent years. Patients with advanced disease might benefit from neoadjuvant therapies, such as perioperative chemotherapy or neoadjuvant chemotherapy with concurrent radiotherapy prior to resection[10, 11]. The CROSS-trial showed an overall 5-year survival benefit of 10% after chemoradiotherapy combined with surgery for patients with esophageal adenocarcinoma, which was not significant[11]. The optimal treatment approach in GEJ adenocarcinoma remains unclear. Currently, the treatment strategy for these tumors depends on the localization of the tumor at preoperative staging and the preference of the surgeon[12]. In general, type I tumors are treated as distal esophageal cancer by means of neoadjuvant chemoradiation according to the CROSS-regimen[11]. Type III tumors are generally treated as gastric tumors which encompasses the use of perioperative chemotherapy[10]. To date, no consensus is yet reached for the optimal approach for type II tumors.

Surgery is the cornerstone of curative treatment. The primary goal of surgery in patients with a resectable adenocarcinoma of the GEJ should be a complete en-bloc removal of the tumor and its affected lymph nodes, with a microscopically tumor-free resection margin (R0-resection), with minimal morbidity and mortality rates. At the same time, a maximal postoperative quality of life must be achieved. To achieve this goal, several types of surgical resections have been introduced throughout the years. These resections include endoscopic ablation or mucosal resection, esophagectomy, gastrectomy or combinations of both. Repeatedly it has been demonstrated that a complete surgical resection is the most important prerequisite for long-term survival in patients with localized esophageal and GEJ cancer[13, 14]. For GEJ adenocarcinoma, the following surgical procedures are widely adopted and currently available: transthoracic esophagectomy with 2-field lymphadenectomy, transhiatal esophagectomy with limited mediastinal lymphadenectomy and total gastrectomy with D1/D2 lymphadenectomy with or without transhiatal resection of the distal esophagus. Furthermore, all procedures can be performed via a minimally invasive or open approach[12]. For type I tumors most surgeons prefer a transthoracic esophagectomy with 2-field lymphadenectomy, while type III tumors are often treated with total gastrectomy with transhiatal resection of the distal esophagus. However, debate continues in determining the optimal treatment approach for true cardiacarcinomas, i.e. type II tumors.

Postoperative complications

Although surgical resection is mandatory for curative treatment of GEJ adenocarcinoma, this comes with a price. With the introduction of minimally invasive techniques and improvements in perioperative care, mortality and morbidity rates have decreased[15]. Nevertheless, the incidence of postoperative complications is still significant. Common complications after surgery are pneumonia, anastomotic leakage and cardiovascular complications. Among them are venous thromboembolic events (VTE) consisting of deep venous thrombosis and pulmonary embolism. In literature, VTE rates up to 13.2% after esophagectomy have been reported[16]. The incidence can be reduced through the use of prophylactic measures such as low-molecular weight heparin, compression stockings and early postoperative mobilization. The use of mechanical prophylaxis including Intermittent Pneumatic Compression has not been investigated before in esophageal and GEJ cancer surgery. Another complication that is getting more and more attention is the development of hiatal hernia (HH) following esophagectomy. A recent systematic review found a mean HH incidence of 2.6%, however this is likely an underestimation due to the limited follow up and also because some studies only documented HH that were treated with surgery[17]. The true incidence and clinical course of HH is still unknown and needs further exploration.

Long-term survival

Despite the increased use of multimodality treatments and improvements in perioperative care, survival of patients with GEJ adenocarcinoma remains poor. Many patients with GEJ cancer develop locoregional recurrence and/or metastatic disease[18, 19]. Tumor infiltration depth, number of metastatic lymph nodes and radicality of resection have often been demonstrated to be associated with poor overall survival, but it remains difficult to predict which patients will develop recurrent disease and which factors are associated with a poor overall outcome. Furthermore, in patients with recurrent disease it is not clear which factors are associated with worse survival and what is the optimal treatment approach in these patients. Further research is required to provide more insight in this patient category.

THESIS OUTLINE

The aim of this research was to evaluate current strategies used for the management of adenocarcinomas of the gastroesophageal junction. In the first part of this thesis, the focus is on the evaluation of current staging tools and treatment strategies including neoadjuvant therapy and surgery. In the second part of this thesis important surgical complications such as venous thromboembolic events and hiatal hernia are addressed. Furthermore, prognostic factors influencing recurrent disease and overall survival in patients are evaluated.

RESEARCH QUESTIONS

The research questions can be summarized as follows:

Part I: staging and treatment

1. What is the value of upper endoscopy/EUS and CT in determining the exact tumor localization and lymph node status in GEJ adenocarcinoma?
2. What is the potential benefit of neoadjuvant chemotherapy prior to surgery in patients with GEJ adenocarcinoma?
3. Should type II tumors preferably be treated with esophagectomy or gastrectomy?
4. What is the optimal treatment strategy for GEJ adenocarcinoma according to population-based data?
5. Is transhiatal esophagectomy a good alternative in patients with a significantly elevated risk for surgery?
6. What is the current status of a minimally invasive approach in transhiatal esophagectomy?

Part II: postoperative course and survival

7. Can venous thromboembolic events after esophagectomy be reduced with the addition of intermittent pneumatic compression to standard thromboprophylaxis?
8. What is the incidence and clinical course of hiatal hernia following esophagectomy and do minimally invasive techniques increase the risk?
9. Is the location of metastatic lymph nodes an important factor for the prognosis of patients with GEJ adenocarcinoma?
10. What are prognostic factors that affect survival in patient with recurrent disease after esophagectomy and what kind of treatment strategies are applied?

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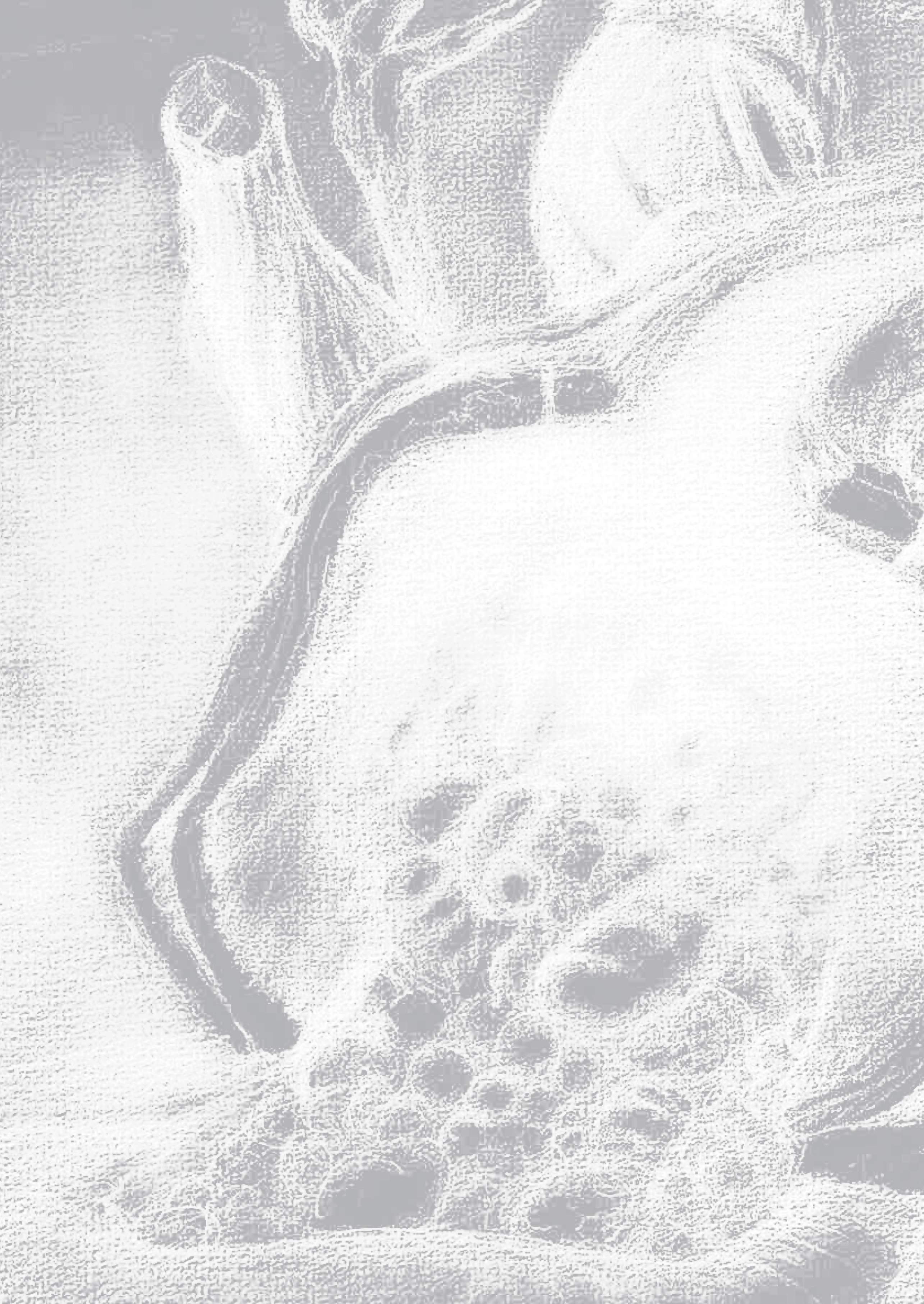

PART I

STAGING AND TREATMENT

Chapter 2

Staging of adenocarcinoma of the gastroesophageal junction.

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European Journal of Surgical Oncology,

2016 Mar; 42(3): 400 – 6

ABSTRACT

Background

Clinical staging of adenocarcinoma of the gastro-esophageal junction (GEJ) determines the curative treatment regimen containing either neoadjuvant chemotherapy or chemoradiotherapy followed by either gastrectomy or esophagectomy. The value of current diagnostic tools is a matter of debate.

Methods

A prospective database (2003-2013) was used to identify 266 consecutive patients with adenocarcinoma of the GEJ in order to evaluate the accuracy of EUS and CT regarding tumor localization according to Siewert, nodal status and its consequences on treatment strategy.

Results

Overall accuracy in determining tumor localization was 73% for EUS and 61% for CT (p=0.018). With EUS, the accuracy was 97%, 66% and 75% for respectively type I, II and III. With CT this was respectively 69%, 57% and 80%. The overall accuracy for determining N-status (N0/N+) per patient was 75% for EUS and 71% for CT. Accuracy for determining a positive nodal station in patients without neoadjuvant therapy was 77% for EUS and 71% for CT (p=0.001). Accuracy for detecting positive upper mediastinal nodes was 80–92%, whereas for peritumoral and abdominal nodes this was 50–80% in both EUS and CT. In 8/266 patients (3%) the type of surgery changed due to intraoperative findings. A radical resection was performed in 233 patients (88%).

Conclusion

Despite the suboptimal accuracy of determining tumor localization with EUS and CT, in only a small number of patients an intraoperative change of surgical treatment was needed. EUS is superior to CT in determining nodal status and tumor localization in GEJ tumors.

INTRODUCTION

The optimal treatment strategy for adenocarcinomas of the gastro-esophageal junction (GEJ) depends on the tumor localization and TNM staging. The administration of neoadjuvant chemoradiation or perioperative chemotherapy and the choice for the surgical approach differs between distal esophageal tumors and subcardial gastric tumors[1-3]. Furthermore, the localization of positive lymph nodes determines the extent of the radiotherapeutic field and lymphadenectomy during surgery[4]. This highlights the importance of accurate diagnostic staging to elaborate an individualized treatment strategy.

Staging of GEJ tumors is performed according to the 7th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) for both gastric and esophageal cancer. GEJ adenocarcinomas are staged according to the esophageal schedule if the tumor extends into the esophagus. Without extension, these tumors are staged as gastric tumors. Pretreatment staging should therefore determine whether the tumor extends into the esophagus or stomach, to choose the appropriate treatment schedule to be used. The most widely used classification system to identify tumor localization is the Siewert classification[5]. Recent studies have demonstrated difficulties in applying the Siewert classification. Discrepancies have been described between preoperative tumor localization as determined by endoscopy/endoscopic ultrasound (EUS) and CT and tumor localization following histopathology[6-9]. Furthermore, several studies have reported that current diagnostic modalities for detection of nodal involvement (EUS, CT and/or PET) have a limited role in predicting positive nodal stations[6, 10]. Despite these limitations of current staging modalities, it is not completely clear what the impact of these limitations is on treatment strategy and outcomes. Therefore, the first aim of this study was to evaluate the accuracy of endoscopy/EUS and CT in determining tumor and lymph node localization of GEJ tumors. The second aim was to evaluate the impact of preoperative assessment on treatment strategy and outcomes.

PATIENTS AND METHODS

A consecutive series of patients (n=266) with histopathological proven adenocarcinoma of the GEJ were included from a prospective database (July 2003 - July 2013). All underwent surgery with curative intent. Diagnostic workup consisted of upper endoscopy combined with EUS, CT scan of the chest and abdomen and ultrasound of the neck. A PET-CT-scan was performed in patients with a suspect lesion on CT or ultrasound of the neck without the possibility for histopathological confirmation. All reports of the upper endoscopy/EUS procedures were reviewed by one of us (KP). CT scans of the chest and abdomen were revised by an experienced gastrointestinal radiologist (RB). The resected specimens were assessed by a pathologist specialized in gastrointestinal pathology (GJAO). The 7th edition of the TNM staging system was used for tumor staging. Institutional Review Board approval was obtained and informed consent was waived for this study.

Tumor localization

During upper endoscopy and EUS, the upper and lower border of the tumor in relation to the anatomic GEJ (defined as the proximal end of the gastric folds) and diaphragm were described. These data were reviewed and tumor localization was defined according to Siewert[5]. Type I which has its epicenter between 1 – 5 cm proximal to the GEJ, type II its epicenter between 1 cm proximal and 2 cm distal to the GEJ and type III its epicenter between 2 – 5 cm distal to the GEJ. In case of large-sized tumors in two or more areas, the tumor was classified as type II, because of the involvement of the esophagus and/or cardia. The radiologist reported the localization of the tumor in relation to the GEJ and diaphragm and defined the tumors according to Siewert. The pathologist reported the upper and lower border of the tumor in relation to the GEJ. Macroscopic photos of resected specimens were reviewed and tumor localization was further determined according to Siewert. The histopathological tumor localization, considered as gold standard, was compared with the tumor localization according to upper endoscopy combined with EUS and CT. A subgroup analysis was performed on patients treated with and without neoadjuvant therapy.

Nodal involvement

The presence of metastatic lymph nodes was analyzed separately in patients treated with and without neoadjuvant therapy. In patients treated with transhiatal esophagectomy or gastrectomy, the abdominal (D1+), paracardial and para-esophageal lymph nodes were analyzed. In patients treated with transthoracic esophagectomy, the upper mediastinal lymph nodes were also analyzed. The following stations were evaluated: paratracheal, aortapulmonary window, subcarinal, para-esophageal, paracardial and lesser curvature, which included the nodes in the hepatoduodenal ligament, along the left gastric and common hepatic artery and around the celiac axis. On EUS a lymph node was considered malignant based on size > 10mm (measured in the long axis), hypoechoic structure, round shape, and sharp or distinct margins. In some patients (n=9), EUS was combined with FNA in case of a suspected lymph node which would alter the treatment approach. Histopathological results of the FNA were separately analyzed. With CT, the radiologist identified suspected lymph nodes according to their size (>5mm for peritumoral nodes and >10mm for other nodes) and the ratio between longitudinal and transverse dimensions (L/T ratio <1.5). At surgery, the paratracheal, subcarinal, para-esophageal and left gastric artery lymph nodes were marked for histopathological analysis. The dissected lymph nodes were counted and analyzed separately according to their localization. The histopathological proven positive nodal stations, considered as gold standard, were compared to suspected nodal stations on EUS and CT.

Treatment strategy

Eligible patients (WHO ≤ 2) with locally advanced tumors (≥T2 or N+) were treated with neoadjuvant therapy according to national guidelines. All patients received perioperative chemotherapy before 1/6/2012[11]. After that, guidelines were changed and patients with an esophageal tumor (type I) received neoadjuvant chemoradiation[12]. Patients with type II tumors received neoadjuvant treatment according to either the esophageal or gastric scheme, dependent on the preoperative assessment and evaluation of these findings in a multidisciplinary expert meeting. In case of surgery, esophagectomy was preferred for type I tumors and gastrectomy for type III. In patients with type II, the surgical approach depended on preoperative findings. A gastrectomy was preferred in case the epicenter of the tumor tended to be in the stomach without esophageal ingrowth. If not, an esophagectomy was preferred. Regarding the type of approach, a transhiatal approach was preferred if a cT1aN0 tumor was present or in case the patient had severe comorbidities (i.e. pulmonary and/or cardiovascular), otherwise the procedure consisted of a transthoracic approach. In case uncertainty remained after the diagnostic workup, the procedure started with a diagnostic laparoscopy to determine whether a transhiatal esophagectomy or gastrectomy should be performed.

Statistical analysis

Analyses were performed using IBM SPSS statistics version 21.0 for Windows. Differences between CT and EUS were compared using the McNemar test. To evaluate differences between patients treated with and without neoadjuvant therapy, the Chi-square test was used. A p-value < 0.05 was considered significant.

RESULTS

A cohort of 266 consecutive patients underwent surgery for adenocarcinoma of the GEJ during the study period. Chemotherapy was given to 48% (127/266) of the patients and chemoradiation in 11% (30/266) (table 1). In total 54% (143/266) were treated with transthoracic esophagectomy, 33% with transhiatal esophagectomy (87/266) and 13% with gastrectomy (36/266). Most patients had a T3 tumor (59%, 158/266) with N+ disease (63%, 168/266). A radical resection (R0) was achieved in 88% (233/266).

Diagnostic workup

In 3/266 patients (1%), the tumor could not be passed by a conventional or pediatric endoscope; in 12/266 patients (5%) an EUS could not be performed due to an obstructing tumor and only the upper mediastinal nodes were analyzed. EUS was not performed in 8/266 patients (3%). All patients had a CT scan. In 18/266 patients (7%), the CT scan was not digitalized and in these patients a comparison between CT findings and histopathology could not be made. A PET-CT scan was performed in 35/266 patients (13%) and none had evidence of distant disease.

Tumor localization

In 16/266 patients (6%), histopathology did not show vital tumor cells in the resected specimens. Two patients had endoscopic mucosal resection prior to surgery and 14 patients had neoadjuvant treatment consisting of chemotherapy (n=11) and chemoradiation (n=3). The original localization of the tumor in complete responders could be estimated in 7 patients due to the presence of scar tissue and so called mucus lakes. In the remaining 7 patients, histopathological tumor localization could not be determined. In 30/266 patients (11%) the tumor could not be identified on pre-treatment CT.

Table 1 Clinicopathological characteristics of 266 patients with adenocarcinoma of the GEJ. Staging was performed according to the 7th edition of the AJCC TNM staging system for both esophageal and gastric cancer.

Characteristic	**Total number N=266**	
Age (median)	63 years	
Male Gender	218	(82%)
ASA – status		
1	68	(26%)
2	158	(60%)
3	38	(14%)
4	1	(<1%)
Neoadjuvant therapy		
No neoadjuvant therapy	108	(41%)
Chemotherapy	127	(48%)
Radiotherapy	1	(<1%)
Chemoradiation	30	(11%)
Type of surgery		
Transthoracic esophagectomy	143	(54%)
Transhiatal esophagectomy	87	(33%)
Total gastrectomy	36	(14%)
T-stage (pT)		
Tis	1	(<1%)
T1	40	(15%)
T2	35	(13%)
T3	162	(61%)
T4	11	(4%)
NM*	17	(6%)
N-stage (pN)		
N0	98	(37%)
N1	59	(22%)
N2	59	(22%)
N3	50	(19%)
M-stage (pM)		
M0	256	(96%)
M1	10	(4%)
Radicality of resection		
R0	233	(88%)
R1 – distal or proximal	3	(1%)
R1 – circumferential	24	(9%)
R1 – both	6	(2%)

* No malignancy found on histopathological analysis due to neoadjuvant therapy (n=14) or prior endoscopic mucosal resection (n=2). ASA = American Society of Anesthesiology.

The overall accuracy for determining tumor localization according to Siewert was 75% with upper endoscopy/EUS (table 2). The accuracy was 97% for type I, 66% for type II and 75% for type III. The accuracy of 66% in type II was mainly due to the large number of cases (n=58, 34%) that were preoperatively classified as type I, but were classified as type II at histopathology. The overall accuracy for CT was 61%, which was significantly lower compared to upper endoscopy/EUS (p=0.018). The accuracy was 69% for type I, 57% for type II and 80% for type III. Also with CT, in patients with a clinical type I tumor 33% had a histopathological type II tumor.

A subgroup analysis was performed to evaluate the influence of neoadjuvant therapy on the accuracy of determining tumor localization. In all patients, staging was conducted before neoadjuvant treatment. The administration of neoadjuvant treatment reduced the overall accuracy of upper endoscopy/EUS (82% vs 70%, p=0.023). This was mainly due to poor classification of type II tumors in patients treated with neoadjuvant therapy (76% vs 60%, p= 0.047). For CT no significant difference was found in the overall accuracy for patients treated with or without neoadjuvant therapy (62% vs 61%, p=0.884).

Table 2 The accuracy of preoperative staging by upper endoscopy/EUS (**2a**) and CT (**2b**) according to the Siewert classification. The histopathological analysis of the resected specimen was considered as the gold standard.

A

Pathology	Endoscopy / EUS				
	Type I	**Type II**	**Type III**	**Total**	**% correct**
Type I	66	2	-	68	97%
Type II	58	114	-	172	66%
Type III	-	4	12	16	75%
Overall				256	75%

B

Pathology	CT				
	Type I	**Type II**	**Type III**	**Total**	**% correct**
Type I	36	16	-	52	69%
Type II	50	86	14	150	57%
Type III	-	2	8	10	80%
Overall				212	61%

Lymph nodes

Analysis was carried out in patients treated without neoadjuvant therapy (n=108, table 3). A total of 417 nodal stations with EUS and 390 nodal stations with CT could be compared to histopathology. The overall accuracy for determining N-status (N0/N+) per patient was 75% for EUS and 71% for CT. In determining a tumor positive nodal station, the overall accuracy was 73% for EUS and 68% for CT ($p=0.001$). In both EUS and CT, the accuracy was best (79%-91%) in the upper mediastinal stations (subcarinal, paratracheal and aortapulmonary window), except for the paratracheal lymph nodes with CT, in which the accuracy was significantly lower for CT compared to EUS (58% vs 91%, $p<0.001$). This was due to a high rate of false positive nodes (34%) on CT. The lowest accuracy was seen for lesser curvature lymph nodes in both EUS and CT, 51 and 53%, respectively. This was mainly due to a high rate of false negative nodes (48%). These data revealed an overall sensitivity and specificity of 0.40 and 0.86 for EUS and respectively 0.31 and 0.84 for CT.

Table 3 Accuracy of EUS and CT in the evaluation of 759 lymph node stations by comparing preoperative imaging with the histopathological analysis of the resected specimen. The upper mediastinal lymph nodes (paratracheal, aortapulmonary window and subcarinal) were only evaluated in patients receiving a transthoracic esophagectomy. The lesser curvature nodes included the nodes in the hepatoduodenal ligament, along the left gastric and common hepatic artery and around the celiac axis. The numbers represent the number of patients in which the status of the lymph node stations (negative or positive) on diagnostic imaging corresponded with histopathology.

Lymph node station	No neoadjuvant therapy (n=108)		With neoadjuvant therapy (n=158)	
	EUS	**CT**	**EUS**	**CT**
Paratracheal	38/43 (89%)	22/38 (58%)	88/95 (93%)	65/97 (67%)
Aortapulmonary window	39/43 (91%)	33/38 (87%)	86/95 (91%)	86/97 (89%)
Subcarinal	34/43 (79%)	30/38 (79%)	79/95 (83%)	82/97 (85%)
Para-esophageal	73/96 (76%)	65/92 (71%)	94/147 (64%)	106/156 (68%)
Paracardial	72/96 (75%)	65/92 (71%)	106/147 (72%)	104/156 (67%)
Lesser curvature	49/96 (51%)	49/92 (53%)	100/147 (68%)	91/156 (58%)
False negative prediction	72/417 (18%)	82/390 (21%)	77/726 (11%)	81/759 (11%)
False positive prediction	40/417 (9%)	44/390 (11%)	96/726 (13%)	118/759 (16%)
Overall accurate prediction	305/417 (73%)	64/390 (68%)	559/726 (76%)	534/759 (70%)

Also an analysis was performed in patients treated with neoadjuvant therapy (n=156, table 3), which showed no significant difference in accuracy for both EUS (73% to 76%, p=0.256) and CT (68% to 70%, p=0.353) compared to non-pretreated patients. In patients with neoadjuvant therapy, the false negative rate decreased with 6% for EUS and 10% for CT. Lymph node downstaging (cN+ to pN0) was present in 30% of the patients according to EUS and 32% of the patients according to CT.

Of the entire cohort, in 3% of the patients (8/266) EUS-FNA was performed of in total 11 nodal stations. Accuracy was 91%. Only 1 patient had a false positive FNA.

Treatment strategy

According to histopathology, 25% (67/266) had type I, 66% type II (176/266), and 6% a type III tumor (16/266). Neoadjuvant chemoradiation was administered in 13% of the patients (9/67) with type I, 11% with type II (20/176) and none with a type III (table 4). In 46% (123/266) the procedure started with a diagnostic laparoscopy to assess the tumor localization. All patients with type I tumors were treated with esophagectomy. In one patient a gastrectomy was planned after diagnostic workup, since the tumor was classified as type II. However, the surgical approach was changed due to intraoperative findings and an esophagectomy was performed. In type II, 88% (155/176) were treated with esophagectomy and 12% with gastrectomy (21/176). In 3% of these patients (6/176), the type of resection was changed from esophagectomy

Table 4 Treatment approach.

	Type I (n = 67)	**Type II (n = 176)**	**Type III (n = 16)**	**UNK* (n = 7)**	**Total (n = 266)**
Primary resection	29 (43%)	70 (40%)	9 (56%)	0	109 (41%)
Resection after neoadjuvant:					
Chemotherapy	29 (43%)	85 (48%)	7 (44%)	4 (57%)	125 (47%)
Chemoradiation therapy	9 (14%)	20 (11%)	0	3 (43%)	32 (12%)
Radiotherapy	0	1 (<1%)	0	0	1 (<1%)
Esophagectomy					
Transthoracic	44 (66%)	94 (53%)	1 (6%)	4 (57%)	143 (54%)
Transhiatal	23 (34%)	61 (35%)	1 (6%)	2 (29%)	87 (33%)
Gastrectomy	0	21 (12%)	14 (88%)	1 (14%)	36 (13%)

*It was not able to determine the histopathological tumor location in 7 patients with complete response after neoadjuvant therapy.

to gastrectomy or vice versa due to intraoperative findings. For type III, 87% (14/16) were treated with gastrectomy and 13% with esophagectomy (2/16). The reason for performing esophagectomy was because these tumors were preoperatively classified as type II tumors. In both patients the procedure started with the thoracic phase and histopathology showed vital tumor cells at the distal resection margin (R1). Furthermore, in another patient with a type III, esophagogastrectomy and colon interposition was planned, however, during the procedure the decision was taken to perform gastrectomy. These data resulted in an overall conversion rate of 3% (8/266) compared to the preoperative staging.

DISCUSSION

The standard diagnostic workup for adenocarcinomas of the GEJ consists of endoscopy, EUS and CT and is used to elaborate an individualized treatment strategy with regard to incorporing neoadjuvant therapy in the treatment plan and the surgical approach[13, 14]. Although recent evidence has shown that these diagnostic modalities have their limitations in the assessment of tumor localization and nodal status, these studies did not address the consequences on the treatment strategy[6-9]. In the present study, accuracy of determining the Siewert classification and lymph node localization was suboptimal, however only a small number of patients needed a change in surgery strategy and in 88% of the patients a radical resection was achieved.

The Siewert classification is primarily based on the epicenter of the tumor in relation to the anatomical GEJ and divides tumors of the GEJ into 3 types[5]. This classification was introduced to address these tumors and to provide guidance in the management. However, several studies reported difficulties in applying the classification and raised questions regarding its value[6-9]. Also in the current study, we have encountered difficulties and found discrepancies between type I and type II in patients treated with and without neoadjuvant treatment. Interestingly, we found that the accuracy of pre-treatment upper endoscopy/EUS significantly decreased when patients were pre-treated. This effect was greatest in type II and may reflect the impact of neoadjuvant therapy on tumor volume. Therefore, histopathological determination of the exact tumor localization may be of limited value in the current era of multimodal therapy. Regarding neoadjuvant therapy, the current guidelines in the Netherlands is to treat patients with adenocarcinomas of the GEJ with preoperative chemoradiation according to the CROSS-regimen if the tumor does not exceed more than 4cm into the stomach[12]. If the tumor does exceed more than 4cm into the stomach or if the tumor primarily is of gastric origin, perioperative chemotherapy according to the MAGIC-scheme is the systemic treatment to prefer[11]. So rather than focusing on the Siewert classification, it would be more useful to evaluate the length of tumor invasion either in the esophagus or stomach and to discuss these findings in a multidisciplinary expert meeting to decide the optimal treatment approach.

Another finding that emphasizes the vital role of a multidisciplinary expert meeting and may demonstrated the limited use of the Siewert classification is that, despite the discrepancies found between the different types, in only a small number of patients (3%) the surgical approach was changed due to intraoperative findings. Moreover, a radical resection was achieved in 88% of the patients, which is comparable to rates reported in literature[3]. It needs to be stressed, however, that the discrepancies between type I and type II resulted in a high rate of esophagectomies at our institution. Nonetheless, we previously reported that there is a considerable prevalence of mediastinal nodal involvement in type II tumors[15]. Esophagectomy (transthoracic and transhiatal) also provides for a more complete lower mediastinal lymphadenectomy and less positive circumferential resection margins[15]. Thus, patients with a type II tumor might benefit from the improved local control of either transthoracic or transhiatal esophagectomy. Nevertheless, we also encountered difficulties in distinguishing type III from type II in a small amount of patients. In result, two patients with a type III tumor were treated with esophagectomy. In both patients the procedure started with the thoracic phase and unfortunately, histopathology showed vital tumor cells at the distal resection margin in both patients. To overcome this problem, we suggest to start with a diagnostic laparoscopy in order to assess the length of tumor extent in the stomach and to decide whether the stomach is suitable for gastric pull-up, in case diagnostic imaging is not conclusive to determine the surgical approach. This can be combined with an intraoperative endoscopy if needed.

Regarding the detection of metastatic lymph nodes, the present study showed that the accuracy of EUS and CT in determining a tumor positive station was best (80 – 90%) for upper mediastinal nodal stations (paratracheal, aortapulmonary window and subcarinal), as has been reported previously[6]. These findings may provide guidance in the decision making of the surgical approach. If there are no suspected lymph nodes upper mediastinal, transhiatal esophagectomy or gastrectomy might be an oncological safe procedure to perform in patients with type II tumors. This was confirmed by a recent study that reported no beneficial effect of a transthoracic esophagectomy in patients with a lymph node negative (N0) adenocarcinoma of the esophagus and GEJ[4]. However, in patients with nodal involvement (N+), a transthoracic esophagectomy significantly improved overall 5-year survival[4]. In regard to nodal stations located para-esophageal, paracardial and at the lesser curvature, the accuracy of EUS and CT decreased to 70-50% in the present study. The main reason for this low accuracy was due to understaging. However, the clinical relevance of these findings may be limited since a full lymphadenectomy of these stations is generally being performed in case of (transhiatal or transthoracic) esophagectomy and gastrectomy.

Since the accuracy regarding tumor localization and nodal status is suboptimal several studies evaluated other diagnostic modalities for this matter. EUS-guided FNA has proven to be more accurate for nodal staging in comparison to EUS alone and CT[16]. However, there are some practical problems with EUS-FNA, as it is not feasible in stenotic tumors or in case lymph nodes are located peritumoral. For these reasons, EUS-FNA was only used in a small number of patients in which the status of EUS-FNA will influence the therapeutic approach in the present study[17]. Furthermore, the role of FDG-PET is becoming more prominent due to its improvements in diagnostic accuracy for detecting distant metastases[10]. However, in the assessment of nodal status, a recent meta-analysis showed a poor pooled sensitivity of 51% (95% CI 34 – 69%) and specificity 84% (95% CI 76 – 91%)[10]. Studies reporting on the role of FDG-PET in determining tumor localization are limited.

In conclusion, the accuracy for determining exact tumor localization with endoscopy/EUS and CT is suboptimal, however only a small number of patients needed a change in surgery strategy. Furthermore, a radical resection was achieved in 88% of the patients. This may suggest that the preoperative evaluation should be based on the length of tumor invasion either in the esophagus or stomach rather than focusing on the Siewert classification.

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Chapter 3

The effect of chemotherapy for patients with an adenocarcinoma of the gastroesophageal junction: A propensity score-matched analysis.

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European Journal of Surgical Oncology, 2016 Jun 29; [Epub ahead of print]

ABSTRACT

Background

The optimal neoadjuvant approach for patients with adenocarcinomas of the gastroesophageal junction (GEJ) remains unclear. Aim of this study was to evaluate the usefulness of perioperative chemotherapy in these patients.

Methods

Consecutive patients with GEJ adenocarcinoma, treated with surgery alone or chemotherapy plus surgery, were included from a prospective database (2003–2013). Propensity score matching was used to build comparable groups. Response to chemotherapy was assessed according to standardized regression grading.

Results

After propensity score matching, 196 patients were included. Chemotherapy was administered in 124 patients (63%). There was no difference between the chemotherapy plus surgery and surgery-alone group regarding overall and disease-free survival (p=0.351 and p=0.529). Pathological good response (i.e. tumor regression grade [TRG] 1-3) was achieved in 32 patients (34%), whereas 81 (66%) had poor response (TRG 4). Good responders had lower ypT-stage (p<0.001), lower ypN-stage (p<0.001) and more R0-resections (100% vs. 78%, p=0.016) compared to surgery-alone patients, which improved the 5-year survival from 35% to 67% (p=0.002). They also developed less recurrences (35% vs. 57%, p=0.048). In poor responders, histopathology did not differ compared to surgery-alone and more recurrences were found (73% vs. 57%, p=0.037). Overall survival in poor responders was 21% compared to 35% in surgery-alone patients (p=0.551).

Conclusion

Perioperative chemotherapy for GEJ adenocarcinoma leads to increased survival in good responders (34%) as compared to surgery alone. Poor responders had no survival benefit and developed more recurrences, which underlines the importance of the search for predictive biological or radiological markers to predict or assess chemotherapy sensitivity.

INTRODUCTION

The optimal multimodality treatment approach for patients with an adenocarcinoma of the gastroesophageal junction (GEJ) is a matter of debate. While several studies advocate the use of neoadjuvant chemoradiotherapy[1, 2], others consider perioperative chemotherapy to be standard of care[3]. A recent meta-analysis demonstrated a survival benefit for both chemotherapy and chemoradiotherapy[4], but trials directly comparing these treatments are limited. Furthermore, the trials included in the analysis of perioperative chemotherapy plus surgery versus surgery alone were all dated before 1996, and most of them only reported on squamous cell carcinoma[4]. Other important trials such as the MAGIC[3], OEO2[5] and FFCD 9703[6] analysed GEJ adenocarcinomas, but included a large number of patients with gastric adenocarcinoma or esophageal squamous cell carcinoma as well. These trials do not provide conclusive insight whether neoadjuvant chemotherapy is advantageous specifically in GEJ adenocarcinomas. The aim of this study was to assess the potential benefit of perioperative chemotherapy in a consecutive series of patients with GEJ adenocarcinoma.

PATIENTS AND METHODS

Data collection

A prospective database of all esophageal and gastric resections at the University Medical Center Utrecht has been maintained since 2003. From 2003-2013 consecutive patients who underwent surgery with curative intent for adenocarcinoma of the GEJ (within

5cm of the anatomical GEJ) were included. Patients with intraoperatively detected metastatic disease (M1) were excluded. For clinical staging and histopathological analysis, the TNM staging system was used. Institutional Review Board approval was obtained and informed consent requirement was waived for this study.

Chemotherapy

Patients were treated with 3 cycles preoperatively and 3 cycles postoperatively with chemotherapy if they had locally advanced tumors (≥T2) or with N+ disease, which consisted of epirubicin 50mg/m2 (intravenously on day 1), cisplatin 60mg/m2 (intravenously on day 1) and capecitabine 625mg/m2 (twice a day orally on days 1-21) (ECX regimen)[3]. In some patients cisplatin was replaced with oxaliplatin 130mg/m^2 (intravenously at day 1) in case of contraindication for cisplatin (nephro- or ototoxicity, arterial thrombosis) (EOX regimen). Reasons for not commencing perioperative chemotherapy were the following: chemotherapy was no part of the treatment protocol (before the year 2008), weight loss >10%, WHO performance status ≥2 or patient request. The dosage was adjusted in case of toxicity and treatment was discontinued in case of unacceptable toxic effects. Postoperative cycles were initiated 6-12 weeks after surgery.

Surgery

Surgery consisted of either transthoracic or transhiatal esophagectomy with gastric tube reconstruction and cervical esophagogastrostomy, or a total gastrectomy. In general, GEJ type I tumors were treated with esophagectomy and GEJ type III with gastrectomy. For type II the surgical approach was primarily dictated by surgeon's preferences based on clinical tumor characteristics. In patients treated with perioperative chemotherapy, surgery was generally scheduled within 3-9 weeks after completion of the last cycle. In patients without neoadjuvant therapy, surgery was generally performed within 6 weeks after diagnosis.

Histopathology

Response to chemotherapy was assessed according to tumor regression grading (TRG) according to the standardized scoring system proposed by Chirieac [7]. TRG 1 represents complete absence of residual cancer, TRG 2 indicates rare residual cancer cells scattered throughout fibrosis, TRG 3 represents residual cancer cells outgrown by fibrosis, and TRG 4 indicates residual cancer cells outgrowing fibrosis[7].

Follow-up

Patients were followed for 5 years after surgery at the outpatient clinic on a regular basis every 3 months in the first year, every 6 months in the second year, and every 12 months afterwards. Follow-up consisted of patient history and physical examination. Radiological imaging was only performed on indication.

Propensity Score Matching

In non-randomized studies, confounding influences of covariates can bias effect estimates. Therefore, propensity score matching was used to build comparable groups and to deal with this confounding bias. Through efficient matching, balance was created as much as possible by calculating the propensity score (defined as the conditional probability of receiving one of the treatments given the following covariates: age, co-morbidity, ASA score, clinical T-stage, clinical N-stage, type of surgery, and clinical Siewert-type). The full propensity score matching technique was used to generate matched sets of cases in which each set may contain one surgery-alone case and one or multiple chemotherapy plus surgery controls and vice versa. Patients that fell outside the joint range of propensity scores (i.e. range of common support) were discarded. After matching, no significant imbalances of observed covariates remained as assessed through univariable analysis.

Statistical analysis

Analysis was carried out with IBM SPSS Statistics (version 21; IBM Corporation, Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages). Continuous variables are presented as median with ranges or means with standard deviations. To evaluate significance of differences between the two groups (surgery alone vs. chemotherapy plus surgery), the chi-square test - or Fisher's exact test in case of small cell count - were used for categorical variables, and the Student's T-test and Mann-Whitney U-test were used for parametric and non-parametric continuous variables, respectively. Survival analysis was performed using the Kaplan-Meier method. Overall survival was defined as the time interval between date of surgery and date of death or last follow-up. Disease-free survival was calculated as the time interval between date of surgery and date of diagnosis of recurrent disease. Survival differences between the two groups were calculated by means of the log-rank test. Furthermore, several subgroup analyses with regard to survival were performed according to clinical T-stage, clinical N-stage, Siewert classification and TRG. At last, a subgroup analysis with regard to histopathology was performed between good and poor responders to preoperative chemotherapy compared to surgery alone. A p-value <0.05 was considered statistically significant.

RESULTS

From a total of 224 eligible patients, perioperative chemotherapy was administered in 125 patients (56%) and 99 (44%) were treated without chemotherapy (Table 1). After propensity score matching a cohort was acquired of 124 patients treated with chemotherapy plus surgery and 72 with surgery alone. All analyses were conducted on the propensity score matched cohort. No significant differences in terms of age, sex, presence of comorbidities, ASA-score, and type of surgery between the two groups were observed (Table 1). Mean age was 63 years (range 38 – 78), and most patients were male (82%). Surgery consisted of a transthoracic esophagectomy in 109 (56%) patients, a transhiatal esophagectomy in 61 (31%) patients, and a total gastrectomy in the remaining 26 (13%) patients. Chemotherapy was administered in 124 patients and consisted of ECX in 86 (70%) and EOX in 23 patients (18%). In 15 patients (12%), ECX was switched during treatment to EOX due to toxic effects.

Histopathological findings

Histopathology revealed a lower pathological T-stage with chemotherapy plus surgery due to downstaging by chemotherapy compared to surgery alone (p=0.005) (Table 2). A median of 19 lymph nodes were resected in the surgery alone group compared to 20 in the chemotherapy group (p=0.503). The chemotherapy group had a lower pathological N-stage with a median number of 1 positive lymph node (range 0–21) compared to 4 nodes (range 0–33) with surgery alone (p=0.002). Of all patients, a radical resection (R0) was achieved in 86%. There were more R1 resections in surgery alone patients (22% vs. 10%, p=0.002). Regarding the response to chemotherapy, 12 patients (10%) had a complete response (TRG 1), 29 (24%) had a partial response (TRG 2-3) and 81 (66%) patients had a poor response (TRG 4) (Table 2). Hence, a good response (TRG 1-3) was achieved in 31 (34%) patients and a poor response (TRG 4) in 81 (66%) patients. In two patients, information on histopathological response was not available and therefore these patients were not addressed as good or poor responders.

Table 1 Baseline characteristics of the original cohort (n=224) and propensity score matched cohort (n=196).

Patient characteristics	**Original cohort**					**Propensity score matched cohort**				
	Surgery alone n=99 (%)		**Chemo + surgery n=125 (%)**		**P value**	**Surgery alone n=72 (%)**		**Chemo + surgery n=124 (%)**		**P value**
Age, years (mean ± SD)	65.4	±10.6	62.8	±8.5	0.031	63.7	±10.5	63.0	±8.3	0.463
BMI, kg/m2 (mean ± SD)	26.1	± 4.3	26.3	±4.0	0.613	26.1	± 4.3	26.3	± 4.1	0.552
Gender					0.378					0.136
Male	83	(84)	99	(79)		63	(87)	98	(79)	
Female	16	(16)	26	(21)		9	(13)	26	(21)	
Comorbidity										
Overall	53	(54)	47	(38)	0.017	37	(51)	47	(38)	0.066
Pulmonary	15	(15)	14	(11)	0.382	13	(18)	14	(11)	0.185
Cardiovascular	25	(25)	24	(19)	0.276	18	(25)	24	(19)	0.353
Diabetes	23	(53)	13	(10)	0.009	14	(19)	13	(11)	0.079
ASA – classification					0.098					0.304
1	23	(23)	29	(23)		19	(27)	29	(23)	
2	53	(54)	85	(68)		37	(51)	84	(68)	
3	22	(22)	11	(9)		15	(21)	11	(9)	
4	1	(1)	0	(0)		1	(1)	0	(0)	
Clinical T-stage		-		-	0.014					0.441
Tis	1	(1)	0	(<1)		0	-	0	-	
T1	17	(17)	1	(17)		6	(8)	1	(1)	
T2	15	(15)	21	(78)		10	(14)	21	(17)	
T3	58	(59)	97	(5)		52	(72)	96	(77)	
T4	8	(8)	6			4	(6)	6	(5)	
Clinical N-stage					0.569					0.542
N0	32	(32)	36	(29)		18	(25)	36	(29)	
N+	67	(68)	89	(71)		54	(75)	88	(71)	
Type of surgery					0.005					0.063
TT esophagectomy	43	(43)	73	(58)		37	(51)	72	(58)	
TH esophagectomy	46	(47)	32	(26)		29	(40)	32	(26)	
Total gastrectomy	10	(10)	20	(16)		6	(8)	20	(16)	
Clinical tumor location					0.394					0.633
Type I	44	(44)	67	(54)		35	(49)	67	(54)	
Type II	50	(51)	53	(42)		35	(49)	52	(42)	
Type III	5	(5)	5	(4)		2	(3)	5	(4)	

BMI = body mass index, ASA = American Society of Anaesthesiology, Tis = carcinoma in situ, TT = transthoracic, TH = transhiatal.

Survival analysis

At the time of analysis, the median duration of follow-up in surviving patients was 57 months (range 15–130). A recurrence developed in 74 patients (60%) treated with chemotherapy plus surgery and in 41 patients (60%) treated with surgery alone. Between both groups no significant difference was observed in location of recurrence (locoregional, distant or both, p=0.601) and median time to recurrence (11 vs. 8 months, respectively; p=0.110). Also, no difference in disease-free survival was observed (median 22% vs. 15% months, p=0.529) (Figure 1A). The overall 5-year survival was 35% in both groups (p=0.351) (Figure 1B).

Several subgroup analyses were performed. No difference regarding overall survival was found in patients with a clinical T3–4a tumor treated with versus without chemotherapy (p=0.304) (Figure 1C). There was no overall survival difference in patients with clinical N+ disease treated with versus without chemotherapy (p=0.363) (Figure 1D). Also, no differences were found in subgroups of patients with a Siewert type I or type II tumor treated with versus without chemotherapy (p=0.253 and p=0.555, respectively) (Figure 1E).

Good and poor responders

Patients with a pathologic complete response (TRG 1) had an improved overall survival compared to surgery alone patients (p=0.003) (Figure 1F). Also patients with a partial response (TRG 2-3) showed a trend towards an improved overall survival compared to surgery alone, although this difference was not statistically significant (p=0.058). There was no difference in overall survival between patients with a poor response (TRG 4) and surgery alone (p=0.494).

According to histopathology, good responders (TRG 1-3) had a significantly lower pT-stage (p<0.001), lower pN-stage (p<0.001) and more radical resections (100% vs. 78%, p=0.016) compared to surgery-alone patients (Table 3). In addition, these patients developed less recurrences (p=0.048). The 5-year survival improved from 35% in the surgery-alone group to 67% in good responders (p=0.002). In poor responders (TRG 4), the pT-stage (p=0.554), pN-stage (p=0.450) and radicality of resection (85% vs. 78%, p=0.237) did not differ from surgery-alone patients (Table 3). Poor responders developed more recurrences compared to the surgery-alone group (p=0.037). The 5-year overall survival in poor responders was 21% compared to 35% in the surgery alone group (p=0.551).

Table 2 Histopathological tumor characteristics between patients treated with surgery alone versus chemotherapy plus surgery in the propensity score matched cohort.

Patient characteristics	**Propensity score matched cohort**				
	Surgery alone n=72 (%)		**Chemo + surgery n=124 (%)**		**P value**
pT-stage (TNM-7)					0.005
T0	1	(1%)	11	(9%)	
T1	10	(14%)	17	(14%)	
T2	3	(4%)	19	(15%)	
T3	51	(71%)	72	(58%)	
T4	7	(10%)	5	(4%)	
pN-stage					0.003
N0	15	(21%)	52	(42%)	
N1	16	(22%)	26	(21%)	
N2	22	(31%)	25	(20%)	
N3	19	(26%)	21	(17%)	
Radicality of resection					0.016
R0	56	(78%)	112	(90%)	
R1	16	(22%)	12	(10%)	
Lymph node yield (median, range)	19	(3-65)	20	(2-57)	0.503
Total positive lymph nodes (median, range)	4	(0-33)	1	(0-21)	0.002
Tumor regression grade					
1	-	-	12	(10%)	
2 – 3			29	(24%)	
4			81	(66%)	

DISCUSSION

This is one of the first reports that analyzed the effect of perioperative chemotherapy in a homogeneous group of patients with GEJ adenocarcinoma. This study demonstrates that only one-third of patients with GEJ adenocarcinoma were pathologic good responders to preoperative chemotherapy. In these good responders, the lower histopathological T- and N-stage along with the improved local control with 100% radicality of resections significantly improved 5-year survival rates compared to surgery-alone patients. However, the vast majority of patients had a poor response with no histopathological downstaging effect nor survival benefit compared to surgery-alone patients. Poor responders even developed more recurrences compared

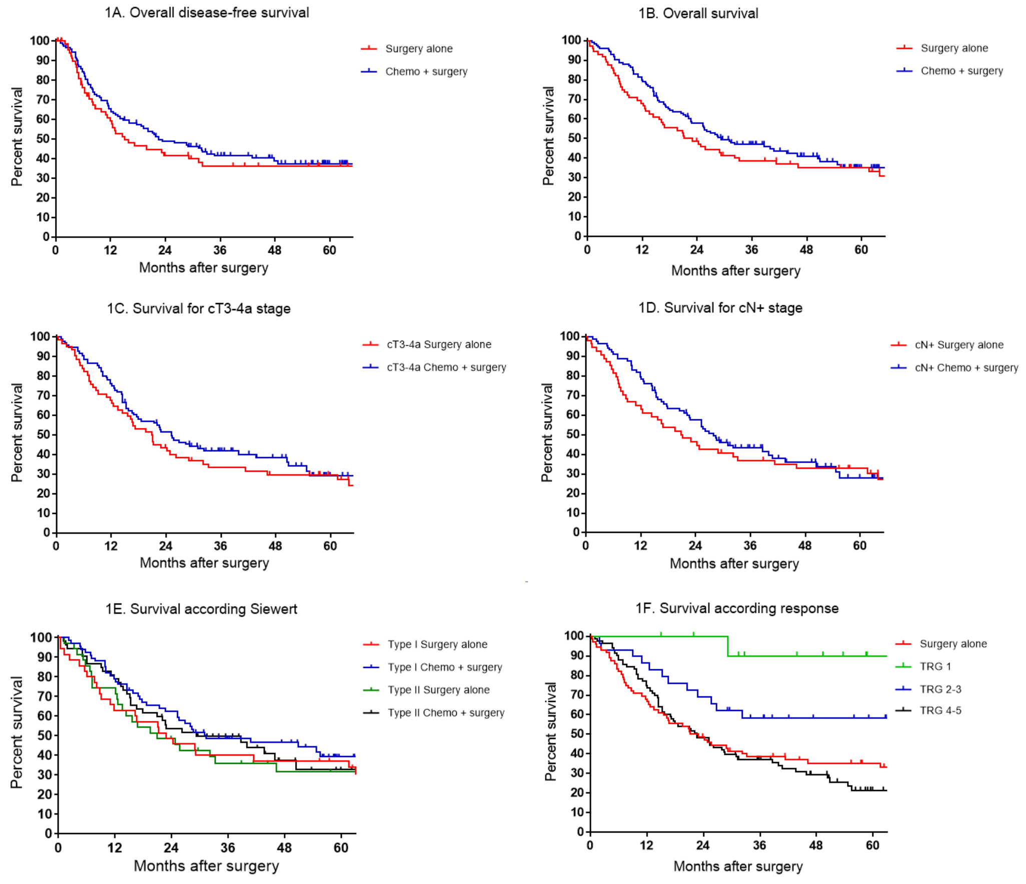
Table 3 Histopathological tumor characteristics and presence of disease recurrence in patients treated with surgery alone compared to good and poor pathological responders in the chemotherapy plus surgery group.

Patient characteristics	Propensity matched cohort							
	1. Surgery alone n=72 (%)		2. Good responders [TRG 1-3] n=41 (%)		3. Poor responders [TRG 4] n=81 (%)		P value 1 vs. 2	P value 1 vs. 3
pT-stage (TNM-7)							<0.001	0.554
T0	1	(1%)	11	(28%)	0	-		
T1	10	(14%)	9	(22%)	7	(9%)		
T2	3	(4%)	7	(17%)	12	(15%)		
T3	51	(71%)	14	(34%)	57	(70%)		
T4	7	(10%)	0	-	5	(6%)		
pN-stage							<0.001	0.450
N0	15	(21%)	27	(66%)	23	(28%)		
N1	16	(22%)	9	(22%)	17	(21%)		
N2	22	(31%)	5	(12%)	20	(25%)		
N3	19	(26%)	0	-	21	(26%)		
Radicality of resection							0.016	0.237
R0	56	(78%)	41	(100%)	69	(85%)		
R1	16	(22%)	0	-	12	(15%)		
Lymph node yield							0.753	0.389
(median, range)	19	(3-65)	20	(5-57)	21	(2-49)		
Total positive lymph nodes							<0.001	0.401
(median, range)	4	(0-33)	0	(0-5)	2	(0-21)		
Recurrence							0.048	0.037
No recurrence	31	(43.1%)	27	(65.9%)	22	(27.2%)		
Locoregional	9	(12.5%)	1	(2.4%)	9	(11.1%)		
Distant	18	(25%)	8	(19.5%)	28	(34.6%)		
Both	14	(19.4%)	5	(12.2%)	22	(27.2%)		

TRG = Tumor regression grade

to the surgery-alone group. Thus, two thirds of the patients may have been treated with surgery alone with equal or even better results, without the toxic effects of chemotherapy. This outcome strongly highlights the importance of moving towards tailored treatment strategies, improving patient outcome and sparing costs associated with the administration of chemotherapy.

Figure 1 Kaplan Meier survival curves in patients treated with surgery alone vs. chemotherapy plus surgery. 1A: Disease-free survival, 1B: Overall survival, 1C: Survival in patients with a clinical T3-4a tumor, 1D: Survival in patients with clinical N+ disease, 1E: Survival according to Siewert type, and 1F: Survival according to pathological response.



In the current study, an overall survival advantage was not observed for patients treated with chemotherapy plus surgery compared to the surgery-alone group. The 5-year survival in both groups was 35%. This is in contrast with some other studies. Patients treated with perioperative chemotherapy in the OEO2-trial experienced an improved 5-year survival from 17% to 23% compared to surgery alone[5]. In the MAGIC-trial the chemotherapy plus surgery patients had an improved 5-year survival of 36% compared to 23% with surgery alone[3]. The greatest advantage was seen in the FFCD9703-trial, in which the addition of chemotherapy improved the 5-year survival from 24% to 38%[6]. However, in contrast to the aforementioned studies and in accordance with this study, the RTOG8911-trial failed to demonstrate a survival advantage with addition of chemotherapy, with 5-year survival rates of 23% in both groups[8]. Similarly, in the RTOG8911-trial a survival advantage was only present in good responders. It is not completely understood what caused the differences between the studies, since all used a cisplatin-based chemotherapy regimen. A possible explanation for the difference between the current and previous studies may be that in this study a favourable R0-resection rate and good survival outcome was achieved in patients treated with surgery alone, underlining the importance of good surgical quality. R0-resection was achieved in 78%, with a 5-year survival of 35% in the surgery-alone group, which is high compared to other series in which R0-resections of 59%-74% and 5-year survival rates of 17%-24% were reported[1, 3, 5, 6].

The 5-year survival in good responders was as high as 67% as opposed to 35% in the surgery-alone group. This impressively improved survival for good responders has been recognized before. Davies and colleagues demonstrated in their series of patients with esophageal and GEJ adenocarcinomas that patients with downstaged tumors had improved radical resection rates and lower rates of isolated local recurrences compared to non-responders[9]. They reported a 5-year survival of 53% in patients with cT3/4N+ who benefitted from a downstaging effect as compared with 13% in the corresponding non-downstaged group. However, also in their study they found that only 44% of the patients responded well to chemotherapy. The remaining 56% actually experienced a worse survival than patients of equivalent stage who underwent surgery alone[9]. In the current study, the 5-year survival was also lower in poor responders (21%) compared to the surgery-alone group (35%), but this difference was not statistically significant. Nevertheless, the significantly increased rates of recurrences in poor responders demonstrates the poor outcome in these patients. A possible explanation for this finding could be that poor responders cope with tumors that are more aggressive by nature. Moreover, the perioperative chemotherapy has no benefit in these patients and only adds up to the overall morbidity, and the curative surgical resection is unnecessarily postponed[10].

These results support the importance of moving towards an individualized treatment strategy. For example, patients with a good response could be offered prolonged systemic therapy[11]. In case of an anticipated pathological complete response, it might even be possible to withhold surgery and follow an active surveillance approach. In contrast, in patients with an anticipated poor response it might be useful to either intensify the treatment or to discontinue chemotherapy during treatment and proceed to early surgery. Furthermore, there is considerable debate whether concurrent radiotherapy in combination with a different chemotherapy regimen (i.e. carboplatin and paclitaxel) results in a more pronounced survival advantage as compared to ECX-chemotherapy alone in GEJ adenocarcinomas. It is well-known that chemoradiotherapy increases locoregional control with high R0-resection rates and higher rates of pathological response[1], however concerns remain of increased surgical morbidity and under-treatment of systemic disease. Future research directly comparing both neoadjuvant treatments should provide insight in the preferred regimen in GEJ adenocarcinomas.

To implement individualized treatment protocols, it is necessary to either accurately predict response prior to the administration of neoadjuvant therapy by use of biological markers and genetic profiling or to accurately measure the response during treatment. Unfortunately, to date there is no clinical study that uses predictive biomarkers in order to identify patients that may benefit from neoadjuvant chemotherapy. Although some biomarkers such as tumor suppressor genes and chemotherapy-associated genes have been identified to predict response to neoadjuvant therapy, they require validation in a large, prospective and homogeneous patient cohort[12, 13]. Current imaging modalities including CT and FDG-PET have limited value in assessing response[14,15]. Endoscopic biopsies or endoscopic ultrasound have also been suggested, but a recent meta-analysis demonstrated insufficient accuracy in predicting pathological response[16]. Thus, it is not yet safe to alter the treatment approach based on the conclusions of these modalities. Future research should focus on predictive biological markers to predetermine individual patients' sensitivity to neoadjuvant therapy and also how to improve response prediction during neoadjuvant therapy to alter the treatment approach if necessary. Diffusion-weighted magnetic resonance imaging seems promising for this purpose in recent pilot studies, but requires validation in larger series[17, 18].

Strengths of the current study are the large, consecutive, and homogeneous series of patients with adenocarcinomas of the GEJ only. Furthermore, this recent series includes the modern-day improvements achieved in upper gastro-intestinal cancer surgery and postoperative care, which is demonstrated by the R0-resection rate of

78% and 5-year survival of 35% in the surgery-alone group. However, some limitations should be addressed. First, while we used the best available method (i.e. propensity score matching) to exclude selection bias as much as possible, this is not a randomized controlled trial and therefore we could particularly not correct for potential unknown confounders. Secondly, we did not carry out a formal sample size calculation to acquire differences between the groups with regard to overall and disease-free survival. However, the differences between the groups are very small. To demonstrate a significant difference, a very large sample size RCT would be needed. Current study demonstrates that only a third of the patients benefit from chemotherapy, and therefore we think future studies should focus on response predication and evaluation to determine who would benefit from chemotherapy, rather than initiating a new properly powered RCT which is accompanied with demanding resources and costs. Lastly, we did not exclude patients in the surgery-alone group who were unsuitable for neoadjuvant therapy due to comorbidities or other causes. We are well aware that these patients would not have been included in a randomized controlled trial. However, one would expect that the difference between the chemotherapy plus surgery and surgery-alone group would have been more distinct in favour of the chemotherapy group with these patients included. However even with this compromised group of patients included in the surgery-alone group, a clear survival advantage for the chemotherapy plus surgery group was not present.

In conclusion, survival after perioperative chemotherapy for adenocarcinoma of the GEJ is highly determined by tumor response. Only 34% of the patients responded well to chemotherapy in this study. As a result of tumor downstaging and improvements in local control, these patients experienced a reduction in the development of recurrent disease and improved survival. Nevertheless, the majority of patients did not benefit from chemotherapy and experienced no survival advantage compared to patients treated with surgery alone. This emphasizes the importance of the search for predictive biological or radiological markers to predict or assess chemotherapy sensitivity to alter the treatment approach if necessary. Future research should focus on these topics to incorporate an individualized treatment approach and improve outcomes in GEJ adenocarcinoma.

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Chapter 4

Surgical treatment of adenocarcinomas of the gastroesophageal junction.

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***Annals of Surgical Oncology*,**
2015 *Feb*; 22(2):597 – 603.

ABSTRACT

Background

Patients with adenocarcinoma of the gastroesophageal junction (GEJ) may undergo either esophagectomy or gastrectomy. Aim of this study was to evaluate the outcome of surgical therapy with regard to postoperative outcome and survival in patients with Siewert type II tumors.

Methods

A prospective database of 266 consecutive patients with surgically resectable GEJ adenocarcinomas from 2003 – 2013 was analyzed. The surgical approach was based on preoperative imaging and intraoperative findings.

Results

According to the histopathological analysis, 67 patients (25%) had type I tumor, 176 patients (66%) type II tumor, and 16 patients (6%) type III tumor. In total 86% were treated with esophagectomy and 14% with gastrectomy. Overall 5-year survival was 38%. In type II patients, the type of operation did not significantly influence overall survival on multivariate analysis (p=0.606). A positive circumferential resection margin at the site of the esophagus was more common with gastrectomy (29% vs 11%, p=0.025). No significant differences in mortality, morbidity or disease recurrence were found. In patients with type II tumors, upper mediastinal nodal involvement (subcarinal, paratracheal and aortapulmonary window) was found in 11% of the patients. In 34% of patients treated with esophagectomy, para-esophageal lymph nodes metastases were harvested compared to 5% of patients treated with gastrectomy.

Conclusion
In patients with a type II GEJ adenocarcinoma, a positive CRM was more common with gastrectomy. Esophagectomy provides for a more complete para-esophageal lymphadenectomy. Furthermore, the high prevalence of mediastinal nodal involvement indicates that a full lymphadenectomy of these stations should be considered.

INTRODUCTION

The incidence of esophageal cancer continues to increase in the Western World. It is now the sixth leading cause of cancer-related mortality and the eight most common cancer worldwide[1, 2]. Adenocarcinoma of the GEJ is defined as a tumor of which the center is within 5cm proximal and distal of the anatomical GEJ (defined by the proximal end of the gastric folds). Siewert et al. divided these tumors into three types based on topographic anatomical criteria of the epicenter of the tumor[3]. Tumors with an epicenter 1 – 5 cm above the GEJ are considered type I, those within 1 cm above and 2 cm below are considered type II and those within 2 – 5 cm below the GEJ are considered as type III tumors[3].

The surgical approach may differ depending on the location of the tumor. Patients with Siewert type I distal esophageal tumors would require an esophageal-cardia resection with two-field lymphadenectomy, while in patients with Siewert type III subcardial gastric tumors a gastric resection is sufficient[4, 4, 5]. The optimal surgical approach in patients with a type II true cardiacarcinoma remains controversial. Some centers prefer esophagectomy, while others prefer total gastrectomy with resection of the distal esophagus[4, 6-9]. The literature does not provide conclusive evidence in the decision making of an esophagectomy or total gastrectomy. Therefore, the aim of this study was to evaluate the outcome of surgical therapy with regard to postoperative course and survival in patients with an adenocarcinoma of the GEJ, with a special interest in type II tumors.

PATIENTS AND METHODS

Patients

A prospective database was used of all patients with surgically resectable esophageal and gastric carcinomas treated at the Department of Surgery at the University Medical Center of Utrecht, the Netherlands from 2003 until present. A consecutive series of patients with adenocarcinoma of the GEJ (n=266), as proven on postoperative histopathological analysis, were included in this study. Adenocarcinoma of the GEJ was defined as a tumor arising within a range of 5 cm of the anatomic GEJ (as defined as the proximal end of the gastric folds).

Treatment

Patients received either neoadjuvant chemoradiation or perioperative chemotherapy. Before the 1st of June 2012, all patients with esophageal or gastric adenocarcinoma received perioperative chemotherapy according to the MAGIC regimen (epirubucin, cisplatinum and 5-Fu)[10] and after that, patients with esophageal adenocarcinoma (type I/II) received chemoradiation according to the CROSS regimen (carbotaxol + 40 Gy) [11]. A subgroup of patients were not eligible for neoadjuvant treatment and primary resection was the treatment of first choice. The surgical approach was based on tumor localization as obtained preoperatively combined with intraoperative findings. For patients with a distal esophageal tumor (type I), an esophagectomy combined with resection of the gastric cardia was performed. Reconstruction was performed with a gastric tube and a left-sided cervical esophagogastrostomy. For patients with a subcardial gastric tumor (type III), a total gastrectomy and D2 lymphadenectomy combined with a transhiatal resection of the distal esophagus was performed. Reconstruction was performed with an esophagojejunostomy using a Roux-en-Y loop. In patients with a true cardia tumor (type II), the decision for either esophagectomy or gastrectomy was based on judgment of the surgeons. If a total gastrectomy was performed, intraoperative frozen sections were obtained from the proximal resection margin. In case the decision for either esophagectomy or gastrectomy could not be made due to non-conclusive preoperative findings, the type of resection was determined intraoperatively.

Histopathological analysis

The resected specimens were assessed by specialized gastro-intestinal pathologists. Stage and grade were classified according to the TNM7 staging system of the AJCC for both gastric and esophageal cancer[12]. The dissected lymph nodes were identified according to their localization, counted and analyzed separately. The resection margin was defined positive (R1) if microscopically the tumor was present at the resection margin, according to the definitions of the College of American Pathologists[13, 14]. In the evaluation of the dissemination pattern of lymph node metastases, analysis of upper mediastinal lymph nodes (subcarinal, paratracheal, aortapulmonary window) was conducted on all patients treated with en bloc esophagectomy with two-field lymphadenectomy. For the analysis of the para-esophageal and abdominal lymph nodes, all patients were included.

Follow-up

Data were collected from date of surgery for a period of 5 years, or until present. Follow up time (in months) was calculated from the date of definitive surgery until the date of death or the date of the last contact with the patient.

Statistical analysis

The data were analyzed using the IBM SPSS statistics version 20.0 for Windows. Continuous variables were expressed as percentages, median (range) and were compared by the Mann-Whitney U test. Ordinal data was compared by the Chi-square or Fisher's exact test. The survival and disease free interval curves were obtained by the Kaplan-Meier method. Differences between groups were assessed by means of the log-rank test. To evaluate independent prognostic factors for survival and disease free interval, multivariate analysis was performed using Cox regression. A p-value < 0.05 was considered statistically significant.

RESULTS

In total 266 patients were treated with a resection of an adenocarcinoma of the GEJ at our institution during the study period. Median age was 63 years (range 38 – 84). Of these patients, 127 (48%) received neoadjuvant chemotherapy and 30 (11%) received neoadjuvant chemoradiation. The clinical patient characteristics are shown in table 1.

Surgical treatment

According to the histopathological analysis, which was considered the gold standard, 67 patients (25%) had a Siewert type I tumor, 176 patients (66%) a type II tumor, and 16

Table 1 Baseline characteristics of 266 patients with adenocarcinoma of the GEJ.

Characteristic	Total	(%)
Median age (range)	63 years (38 – 84)	
Gender		
Male	218	(82)
Female	48	(18)
ASA – status		
1	68	(26)
2	158	(60)
3	38	(14)
4	1	(0,4)
Neoadjuvant therapy		
No neoadjuvant therapy	108	(41)
Chemotherapy	127	(48)
Radiotherapy	1	(0,4)
Chemoradiation therapy	30	(11)
Barrett's metaplasia		
Yes	134	(50)
No	132	(50)

Table 2 Surgical approach based on the histopathological Siewert classification.

	Type I (n = 67)	**Type II (n = 176)**	**Type III (n = 16)**	**NM[a] (n = 7)**	**Total (n = 266)**
Primary resection	29	68	9	1	107
Resection after neoadjuvant therapy	38	108	7	6	159
Esophagectomy					
Transthoracic	44	94	1	4	143
Transhiatal	23	61	1	2	87
Gastrectomy	0	21	14	1	36

[a] No malignancy found on histopathological analysis due to neoadjuvant therapy or prior endomucosal resection.

patients (6%) a type III tumor. Table 2 shows the distribution of the surgical procedures performed. All patients with a Siewert type I tumor received an esophagectomy. In patients with a type III tumor, 14 patients (88%) received a total gastrectomy. The other 2 patients received an esophagectomy. In patients with a type II tumor, a total number of 155 patients (88%) received an esophagectomy. The remaining 21 patients (12%) were treated with gastrectomy. At multivariate analysis, there was no significant difference in the distribution of age, ASA-scores or neoadjuvant therapy between esophagectomy and gastrectomy. In the gastrectomy group there was a higher percentage of females (31% versus 16%, p = 0.036).

Postoperative course

The postoperative course is shown in table 3. The overall in-hospital mortality rate was 3.8%. A subgroup analysis was performed in patients with a type II tumor. There were no significant differences in the morbidity rate, mortality rate, total median time in ICU and total duration of hospital stay between esophagectomy and gastrectomy.

Table 3 Postoperative course

	Overall (n = 266)	**Type II (n=176)**		**p-value**
		Esoph[a] (n = 155)	**Gastr[b] (n = 21)**	
Hospital mortality	10 (3,8%)	4 (2,6%)	1 (4,8%)	0.474
< 30 days	6 (2,3%)	3 (1,9%)	1 (4,8%)	0.401
> 30 days	4 (1,5%)	1 (0,6%)	0	1.000
Time in ICU (days)				
Median (Range)	1 (0 – 136)	1 (0 – 136)	1 (0 – 25)	0.236
Hospitalization (days)				
Median (Range)	15 (3 – 82)	16 (3 – 182)	16 (7 – 64)	0.723
Overall Morbidity	192 (72%)	119 (77%)	14 (67%)	0.312
Pneumonia	116 (44%)	69 (45%)	6 (29%)	0.166
Anastomotic leakage	72 (27%)	44 (28%)	5 (24%)	0.661
Mediastinitis	24 (9%)	11 (7%)	3 (14%)	0.224
Sepsis	22 (8%)	9 (6%)	2 (10%)	0.623

[a] Esophagectomy

[b] Gastrectomy

Histopathological analysis

The histopathological analysis of the resected specimen is shown in table 4. In 87% of the patients a complete tumor removal (R0) was achieved. The majority of the patients were diagnosed with ≥ T3 (65%) tumors and N+ disease (63%). A subgroup analysis was performed on patients with a type II tumor. In the gastrectomy group there were significantly more positive circumferential resection margins (CRM, 29% versus 11%, p=0.025) at the site of the esophagus. There were more advanced tumors (T4) and more lymph node metastases (N3) in patients treated with gastrectomy (T4: p=0.023 and N3: p<0.001), whereas in patients treated with esophagectomy lymph node metastases was less common (N0, p=0.049). Median number of harvested lymph nodes was 19 for esophagectomy and 16 for gastrectomy (p=0.523).

Survival

Follow-up data were available for all 266 patients. The median length of follow up in surviving patients was 26 months (range 2 – 115). The overall median length of survival was 26 months (95% CI: 20 – 32). Overall 5-year survival was 38%. Multivariate analyses, conducted on all patients, showed that the long-term survival rate was independently determined by nodal status (N0 – N3; p<0.001), radicality of the resection (R0 – R1; p=0.005) and tumor infiltration depth (T1 – T4; p=0.009, figure 1). For the analysis of the disease free survival, patients with in hospital mortality were excluded. Nodal status (N0 – N3; p < 0.001), tumor infiltration depth (T1 – T4; p=0.002), radicality of the resection (R0 – R1; p=0.024) and treatment with neoadjuvant therapy (p=0.046) were independent prognostic factors. Overall recurrence rate was 46% after median follow up time of 26 months (range 2 – 116). Median time to recurrence was 9 months.

Subgroup analysis was performed on patients with a type II tumor. The overall median length of survival was 29 months (95% CI: 18 – 41). Overall 5-year survival in patients treated with esophagectomy was not significant on multivariate analysis (p=0.606). Furthermore, there were no significant differences in disease free survival and recurrence rate between the type of surgery performed (p=0.251 and p=0.669).

Lymph node metastases

As seen in figure 2, the majority of the positive lymph nodes were found at the lesser curvature, (43% in type I and 56% in type II) and paracardial (7% in type I and 24% in type II). In patients with a type II tumor treated with transthoracic or transhiatal esophagectomy, 32% and 36% respectively had lymph node metastases in the para-

Table 4 Histopathological tumor characteristics.

Parameters	Overall (n=266) in %	Type I (n=67) in %	Type II (n=176) Esoph (n=155) in %	Type II (n=176) Gastr (n = 21) in %	Type III (n=16) in %	p-value
pT-stage						
Tis	1	1	1	0	0	1.000
T1	15	33	11	0	6	0.229
T2	13	16	15	0	6	0.080
T3	61	49	67	81	56	0.199
T4	4	0	2	14	31	0.023
NMa	6	1	5	5	0	1.000
pN-stage						
N0	37	39	37	14	25	0.049
N1	22	34	19	19	13	1.000
N2	22	15	28	14	13	0.200
N3	19	12	15	52	50	0.000
pM-stage						
M0	96	99	96	100	81	1.000
M1	4	1	4	0	19	
R0-resection	87	91	87	71	13	0.058
R1 – distal or proximalb	3	2	4	5	6	0.596
R1 – circumferentialc	12	9	11	29	13	0.025
Median number of harvested lymph nodes (range)	18 (2-65)	18 (3-57)	19 (2-65)	16 (3-53)	19 (5-35)	0.523
Median number of positive lymph nodes (range)	2 (0-33)	1 (0-20)	2 (0-21)	7 (0-33)	7 (0-29)	0.002

[a] No malignancy found on histopathological analysis due to neoadjuvant therapy or prior endomucosal resection.
[b] Microscopically presence of tumor at the proximal or distal resection margin.
[c] Microscopically presence of tumor at the esophageal circumferential resection margin.

esophageal nodes. However, in those treated with gastrectomy, only 5% had para-esophageal nodes on histopathological analysis. Upper mediastinal nodal involvement (subcarinal, paratracheal, aortapulmonary window), was present in 11% of the patients with a type II tumor, whereas it was present in 25% of patients with a type I tumor (p = 0.020). Furthermore, upper mediastinal nodal involvement in patients with at least one positive lymph node (N+ disease), was present in 22% of the patients with a type II tumor.

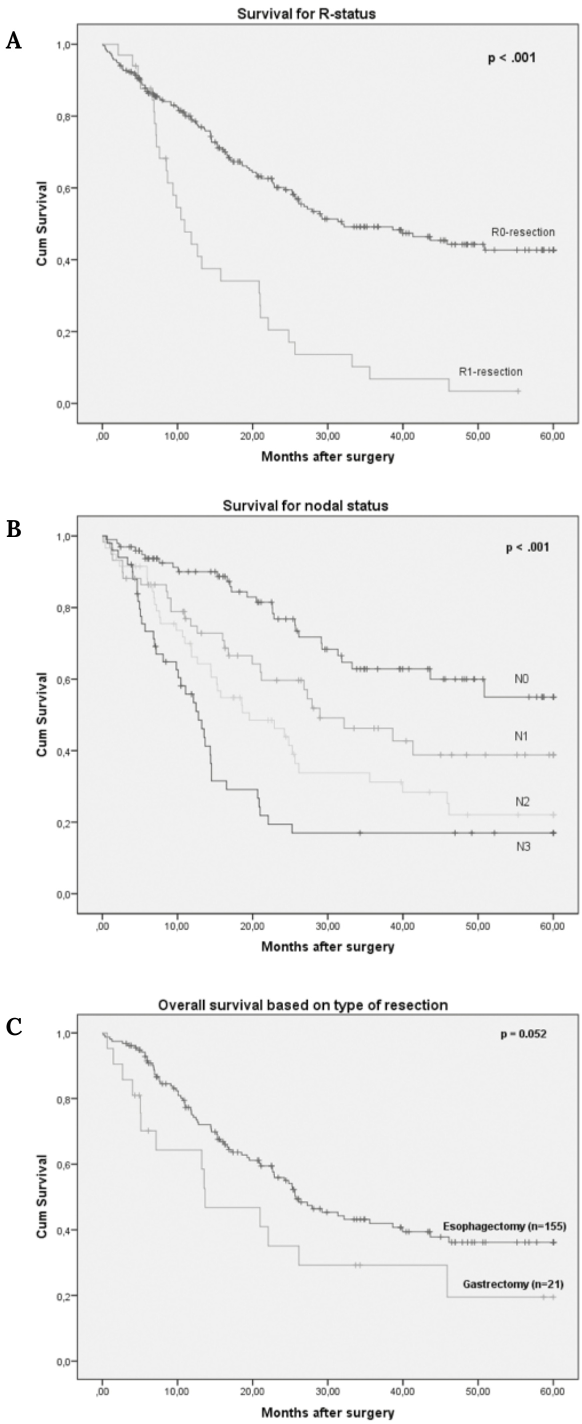
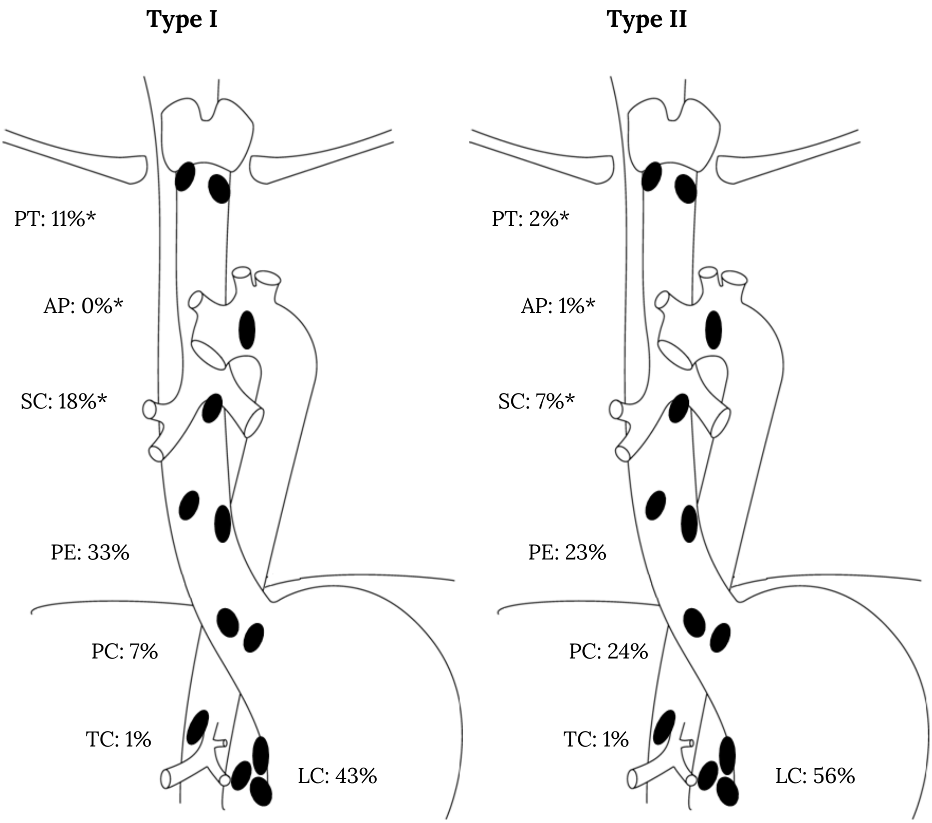


Figure 1 Effect of the radicality of the resection (R0-R1, **1A**) and nodal status (N0-N3, **1B**) on the overall 5-year survival rates of all 266 patients with adenocarcinoma of the GEJ. The overall 5-year survival dependent on the type of resection in patients with a Siewert type II tumor on univariable analysis (**1C**, n=176).

Figure 2 Spread pattern of lymph node metastases on histopathological analysis in Type I and Type II patients. The upper mediastinal lymph nodes were analyzed for all patients treated with en bloc esophagectomy and two-field lymphadenectomy (n = 111). The para-esophageal and abdominal lymph nodes were analyzed in all patients.



PT = paratracheal, AP = aortapulmonary window, SC = subcarinal, PE = para-esophageal, PC = paracardial, TC = celiac trunk, LC = lesser curvature (contained omentum minus and left gastric artery). *Upper mediastinal nodal involvement (PT, AP and SC) was present in 25% of the patients with a type I tumor and 11% of the patients with a type II tumor.

DISCUSSION

Several studies have been performed to evaluate survival differences between esophagectomy and gastrectomy in patients with a type II tumor[4, 6, 7, 9, 15-17]. A broad consensus has not yet been achieved and the type of surgery is still a subject of debate. In this single center cohort study a consecutive of 266 patients with adenocarcinoma of the GEJ were analyzed. A special focus was given on patients with Siewert type II tumors to determine a possible difference between an esophagectomy or a total gastrectomy. This study did not show a significant difference in overall 5-year survival between the type of surgery performed in patients with a type II tumor. However, the presence of a positive circumferential resection margin was significantly more common in patients treated with gastrectomy. Furthermore, upper mediastinal nodal involvement was present in 11% of the patients. These findings indicate that transthoracic esophagectomy should be the procedure of choice in most patients with a type II tumor.

One of the strongest independent prognostic factors for overall survival is the presence of metastatic lymph nodes (N+)[6-9, 16, 18], which was confirmed in this study. Several studies, including this, report that the stations with the most affected lymph nodes are the paracardial and lesser curvature stations[8, 19, 20]. A full lymphadenectomy of these stations is therefore crucial and is generally performed in both esophagectomy and gastrectomy. However, this study showed that esophagectomy provides for a more complete lymphadenectomy of para-esophageal nodes compared to gastrectomy. The number of metastases in para-esophageal nodes was present in 34% of the patients treated with esophagectomy and only in 5% of the patients treated with gastrectomy. This low amount of metastases might be the result of a less extensive lymphadenectomy of the para-esophageal nodes. Siewert et al. mainly performed gastrectomy in type II tumors but also acknowledged the necessity of a lower mediastinal lymphadenectomy and perform wide splitting of the esophageal hiatus[17]. However, the presence of metastases in the para-esophageal nodes in patients with N+ disease is remarkably lower (15,6%) than in this study (67%) and could indicate that in the present study a more extensive lymphadenectomy is performed with esophagectomy. A possible explanation could be that even with wide splitting of the hiatus, it is very difficult to perform an adequate dissection into the mediastinum, especially to reach the higher para-esophageal lymph nodes, suggesting the beneficial effect of an esophagectomy in these patients

Furthermore, our findings of upper mediastinal nodal involvement (subcarinal, paratracheal and aortapulmonary window) in 11% of the patients with type II tumors indicates that also a full lymphadenectomy of these stations should be considered to ensure a complete en-bloc tumor removal and its affected lymph nodes, especially since diagnostic modalities for the detection of nodal involvement (EUS and or PET/CT) have limited value in predicting tumor presence in these lymph nodes[21, 22]. The benefit of extended surgery is acknowledged by a study that compared the extended transthoracic approach versus limited transhiatal resection in T3N1 tumors of the GEJ[23]. The survival significantly improved with transthoracic en bloc esophagectomy when there were 8 or fewer involved lymph nodes. In case more lymph nodes were affected, survival was poor and independent of the type of resection.

An extensive lymphadenectomy provides removal of both known and unknown metastatic lymph nodes. This is acknowledged by the fact that previous studies reported that survival improves with an increasing number of lymph nodes removed[24-26]. Not only was this effect seen in patients with N+ disease, but also an improved survival after extensive lymphadenectomy was demonstrated in patients with no lymph nodes involved[26, 27].

The presence of tumor at the proximal resection margin is an independent prognostic factor associated with a poor overall survival GEJ[28]. Several studies suggested that a resection margin of up to 10 cm is necessary to prevent local recurrence[28-30]. A large study reported that the overall survival significantly improved when the proximal margin length of the resected specimen was greater than 3.8 cm in T2 or greater tumors (in situ length 5 cm)[9]. This length is very difficult to achieve with gastrectomy, since the possibility to gain adequate length with a transhiatal resection of the distal esophagus is limited. Also for a positive circumferential resection margin (CRM) a poorer prognosis was described[31]. This was significantly more common in type II patients treated with gastrectomy in our study. In the patients with a positive CRM in type II tumors, it was always at the esophageal CRM, which indicates that with gastrectomy it is more complicated to adequately dissect the distal esophagus. The extensiveness and quality of the dissection improves with esophagectomy. These results support the routine use of esophagectomy not only to provide for a more complete mediastinal lymphadenectomy but also to provide for a radical dissection of the esophagus in patients with type II tumors.

In conclusion, a positive CRM was more common with gastrectomy in patients with a type II GEJ adenocarcinoma. Esophagectomy provides for a more complete para-esophageal lymphadenectomy. Furthermore, the high prevalence of mediastinal nodal involvement indicates that a full lymphadenectomy of these stations should be considered in type II tumors.

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Chapter 5

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

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***Annals of Surgical Oncology*, 2016 May; 23(5):1632 – 8.**

ABSTRACT

Background
Resectable gastroesophageal 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
A total of 3450 patients underwent parathyroidectomy, of which 84 patients with recurrent (n=10) or persistent disease (n=74) and 41 patients with primary surgery were included. MRI had a sensitivity and PPV of 79.9% and 84.7%, respectively, and performance was good in both patients with- and without previous parathyroid surgery. Adding MRI to the combination of ultrasound and sestamibi resulted in a significant increase in sensitivity from 75.2% to 91.5%. Dynamic MRI performed excellent in the re-operative group with sensitivity and PPV of both 90.1%.

Conclusion
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

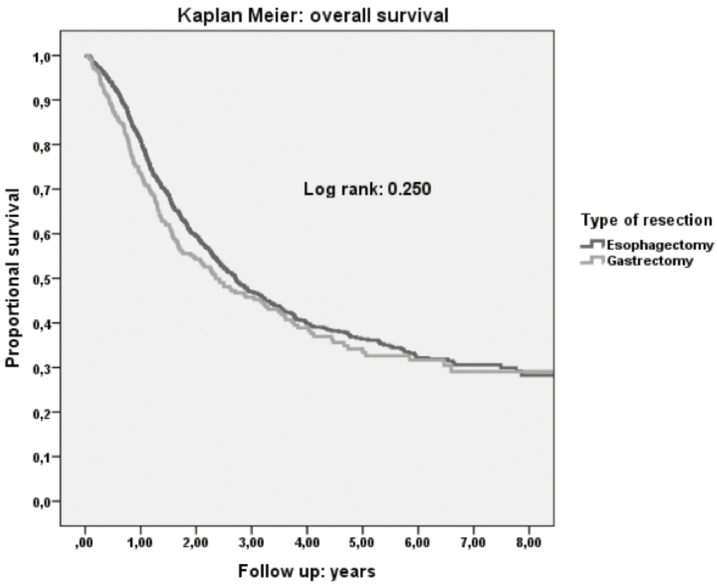
Between January 2005 and December 2012, 4050 patients were diagnosed with an adenocarcinoma of the GEJ in the Netherlands. Patients with metastatic disease (n=1620) or unknown/missing M-status (n=307) were excluded. Furthermore, 149 patients with tumors infiltrating surrounding organs (T4) were excluded 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.

Figure 1 Overall survival of patients with a resectable adenocarcinoma of the GEJ treated with 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



RESULTS

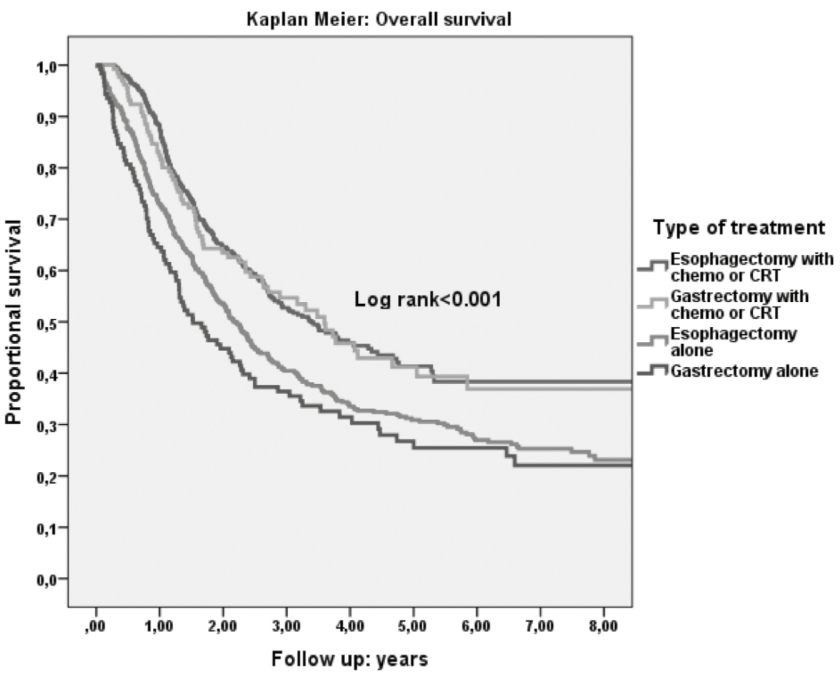
A total of 1196 patients with resectable and potentially curable adenocarcinoma of the GEJ treated with a surgical resection were evaluated. Mean age was 64.4 years (SD 10.4) (Table 1). The majority of the patients were male (80%). Most patients were clinically diagnosed with a T3 tumor (n=520, 43%) 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

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



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).

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%, $p=0.323$).

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 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				0.036
Male	954 (79.8%)	761 (81.0%)	193 (75.1%)	
Female	242 (20.2%)	178 (19.0%)	64 (24.9%)	
cT stage				<0.001
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%)	
cN-stage				<0.001
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%)	
Perioperative therapy				<0.001
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%)	

Table 2 Histopathological characteristics.

	Esophagectomy (n=939, 78.5%)	Gastrectomy (n=257, 21.5%)	p-value
Tumor differentiation			0.308
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%)	
Tumor stage[a]			0.056
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%)	
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]			0.217
R0	786 (86.7%)	209 (83.6%)	
R1/2	121 (13.3%)	41 (16.4%)	

[a] Exclusion of unknown (n=29), [b] Exclusion of unknown (n=23), [c] Exclusion of unknown (n=19),
[d] Exclusion of unknown (n=39)

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

Table 3 Multivariable Cox regression analysis on overall survival.

		Univariable			Multivariable		
Number of patients (n=1196)	**N**	**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

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 an 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 6

The selective use of transhiatal esophagectomy for patients with an elevated risk for surgery offers a chance for cure.

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Submitted

ABSTRACT

Background

To evaluate the postoperative course and survival in patients with a significantly elevated risk for surgery treated with transhiatal esophagectomy.

Methods

A prospective database was used for analysis. High-risk patients were those with an American Society of Anaesthesiologists (ASA) score ≥ 3, severe lung- and cardiovascular comorbidities, age ≥ 80 and emergency esophagectomy. Multivariate analysis was conducted to determine prognostic factors for the development of complications.

Results

The database included 68 high-risk patients treated with THE. Mean age was 69 years and 87% had pre-existing comorbidities. In 37% neoadjuvant therapy could be administered. A radical resection was achieved in 87%. A postoperative complication occurred in 45 patients (66%), which included anastomotic leakage in 24 (35%), pneumonia in 23 (34%) and atrial fibrillation in 15 patients (22%). In 24 (35%) patients a major complication occurred requiring Intensive Care treatment or surgical intervention (Clavien–Dindo grade ≥ 3). Median ICU time and hospital stay were respectively 2 and 19 days. In-hospital mortality was 3% and overall 5-year survival was 36%. Increasing age was associated with the development of major complications on multivariate analysis (OR= 1.075, 95%CI=1.003 – 1.153, p=0.042).

Conclusion

Transhiatal esophagectomy is a good surgical alternative for high-risk patients offering a significant chance for cure.

INTRODUCTION

In patients with esophageal cancer, multimodality treatment including neoadjuvant therapy and surgical resection is the standard of curative care [1,2]. For locally advanced tumors, a transthoracic esophagectomy (TTE) with 2-field lymphadenectomy is the preferred approach, offering a thorough mediastinal lymph node dissection [3]. However, TTE is complex surgery and is associated with high postoperative morbidity[4]. Furthermore, it is unsuitable for high-risk patients who have extensive comorbid disease and a significantly elevated risk for postoperative complications associated with thoracotomy and single lung ventilation. Transhiatal esophagectomy (THE), which avoids a thoracotomy, has been proven to reduce postoperative morbidity [5,6]. Hence, THE might offer a chance of cure for high-risk patients. At our institution, THE has been the preferred approach for patients with an elevated surgical risk, having multiple comorbidities such as pulmonary or cardiovascular disease and/or a poor performance status [7,8]. Those with advanced age (≥ 80 years) have an additional risk of mortality and morbidity and are also considered to be high-risk patients[9].

Therefore, this observational cohort study was conducted to evaluate the postoperative course and overall survival in patients with a significantly elevated risk for surgery treated with transhiatal esophagectomy for cancer of the esophagus or gastroesophageal junction (GEJ).

PATIENTS AND METHODS

Study population

Consecutive patients treated with THE between July 2005 and May 2014 were included from the prospective database of the University Medical Center Utrecht. All were diagnosed with clinical resectable esophageal or GEJ cancer (cTis-T4a) without evidence of metastatic disease (cM0). Workup consisted of a physical examination, routine blood tests, upper endoscopy, endoscopic ultrasonography (EUS), computed tomography (CT) of the chest and abdomen and evaluation of the pulmonary function. A positron emission tomography (PET) was performed on indication. Clinical and histopathological oncological status was classified according to the seventh edition of the UICC TNM staging system. Tumor biology and patient characteristics were evaluated in a multidisciplinary meeting to elaborate the optimal treatment strategy. Informed consent requirement was waived by the Institutional Review Board.

Treatment

Eligible patients (WHO ≤ 2) with locally advanced tumors (≥T2 or N+) were pre-treated according to the national cancer guidelines and consisted of either neoadjuvant chemotherapy (epirubicin, cisplatin and 5-fluorouracil) or neoadjuvant chemoradiation (carboplatin, paclitaxel and 41.1Gy). Surgery was performed by either open or laparoscopic THE followed by gastric tube reconstruction and left-sided cervical anastomosis. There were two main reasons for choosing a transhiatal approach; either patients had an elevated risk for surgery due to comorbid disease (high-risk group) and therefore not considered eligible for transthoracic esophagectomy or patients had an early (cTis-1N0) or distal tumor (Siewert type II) without evidence of mediastinal dissemination in which case a transhiatal esophagectomy was performed. Patients treated for early or distal tumors were excluded from the analysis. High-risk was defined as an American Society of Anaesthesiologists (ASA) score ≥ 3, severe comorbidities (i.e. pulmonary and/or cardiovascular), age ≥ 80 years and emergency esophagectomy.

Postoperative course

Postoperative outcomes were defined in terms of postoperative complications, time in the Intensive Care Unit (ICU), length of hospital stay and in-hospital mortality (IHM). These outcomes were prospectively collected in our database. Complications included anastomotic leakage, pneumonia, atrial fibrillation, wound infection, pneumothorax, chyle leakage and thrombo-embolic event. Anastomotic leakage was defined as any radiological or clinical evidence of leakage regardless of the required treatment. Pneumonia was defined according to the Utrecht Pneumonia Score (UPS)[10]. The acquired postoperative complications were graded according to the Clavien-Dindo Classification (CDC).

Statistical analysis

IBM SPSS statistics version 23.0 for Windows was used to conduct all analyses. Survival curves were obtained using the Kaplan-Meier method, and the log-rank test was used to identify differences between groups. Multivariate analyses were performed to identify prognostic factors for postoperative morbidity. Only variables with a p-value ≤ 0.200 on univariable analysis were considered for multivariate analysis. A p-value < 0.050 was considered statistically significant.

RESULTS

Study population and histopathological characteristics

A total of 104 consecutive patients with cancer of the esophagus or GEJ were treated with THE with curative intent (cTis-4aN0-3M0), of which 36 (35%) were treated with THE for early or distal tumors. These patients were excluded from the analysis. The remaining 68 patients were treated with a THE because of high perioperative risk. Table 1 demonstrates the clinical and histopathological characteristics of the study population. Mean age was 69 years (standard deviation [SD] 9.8) and most patients were males (n=52, 77%). The majority had an ASA-score of 2 (n=36, 53%) or 3 (n=28, 41%). Overall, 59 patients (87%) had pre-existing comorbidities, which included vascular disease (n=39, 57%), cardiac disease (n=31, 46%) and pulmonary disease (n=26, 38%). Neoadjuvant chemotherapy was given to 14 (21%) and neoadjuvant chemoradiation to 11 patients (16%). Neoadjuvant treatment was not administered in 43 patients (63%) because of the following reasons: WHO performance status > 2 (n=20, 29%), early-staged disease (n=6, 9%), >10% weight loss (n=3, 4%), not part of treatment protocol (n=5, 7%), emergency surgery (n=3, 4%), patients request (n=2, 3%) or other (n=4, 6%). A laparoscopic approach was performed in 42 patients (62%). Most patients had an adenocarcinoma (n=56, 82%) at the GEJ (type 2, n=39, 57%) with stage III disease (n=32, 47%). A median number of 16 lymph nodes were resected during surgery. A radical resection was achieved in 59 patients (87%).

Postoperative course

A postoperative complication occurred in 45 patients (66%, Table 2). Anastomotic leakage was the most common complication, which occurred in 24 patients (35%). In most patients the leakage could be treated by opening the cervical wound and a nil per os strategy. In 4 patients with anastomotic leakage (17%), a reoperation was required. A pneumonia occurred in 23 patients (34%), whereas atrial fibrillation occurred in 15 patients (22%). The overall reoperation rate in the entire cohort was 16%. Of all patients, 24 (35%) developed a major complication that required Intensive Care treatment or surgical intervention (Clavien–Dindo grade ≥ 3). Median ICU time and hospital stay were respectively 2 and 19 days. The in-hospital mortality rate was 3% (n=2). One patient died from sepsis and multi-organ failure due to pericarditis and the other died from respiratory insufficiency after a major cerebral vascular accident.

Table 1 Clinical and histopathological characteristics of all patients

	All patients (n=68)
Age (mean ±SD)	69y (± 9.8)
Male gender	52 (77%)
BMI (mean ±SD)	25 (± 4.3)
ASA – classification	
1	3 (4%)
2	36 (53%)
3	28 (41%)
4	1 (2%)
History of malignancy	16 (24%)
Comorbidities	
Overall	59 (87%)
Pulmonary	26 (38%)
Cardiac	31 (46%)
Vascular	39 (57%)
Diabetes	20 (29%)
Neurologic	15 (22%)
FEV1	
≥ 85%	36 (53%)
>75%< 85%	9 (13%)
≤75%	15 (22%)
Unknown	8 (12%)
Neoadjuvant therapy	
None	43 (63%)
Chemotherapy	14 (21%)
Chemoradiation	11 (16%)
Type of surgery	
Open	26 (38%)
Laparoscopic	42 (62%)

	All patients (n=68)
Histology	
Carcinoma in situ	2 (3%)
Adenocarcinoma	56 (82%)
Squamous cell carcinoma	10 (15%)
Tumor Location	
Proximal	1 (2%)
Mid	3 (4%)
Distal	25 (37%)
Junction	39 (57%)
Stage	
0	7 (10%)
I	12 (18%)
II	17 (25%)
III	32 (47%)
IV	-
Total harvested lymph nodes (median, range)	16 (3 – 35)
Total positive lymph nodes (median, range)	1 (0 – 17)
Completeness of resection	
R0	59 (87%)
R1-proximal / distal	1 (2%)
R1-circumferential	5 (7%)
R1-both	3 (4%)

SD = standard deviation, BMI = body mass index, ASA = American Society of Anaesthesiology, FEV1 = forced expiratory volume in 1 second [% of predicted value].

Table 2 Postoperative course and follow up

	High-risk patients (n=68)
Morbidity	
Any complication	45 (66%)
Anastomotic leakage	24 (35%)
Pneumonia	23 (34%)
Atrial fibrillation	15 (22%)
Wound infection	7 (10%)
Pneumothorax	6 (9%)
Thrombo-embolic event	4 (6%)
Chyle leakage	4 (6%)
Reoperation	11 (16%)
Clavien–Dindo classification	
No complication	23 (34%)
Grade 1	5 (7%)
Grade 2	16 (24%)
Grade 3	4 (6%)
Grade 4	18 (27%)
Grade 5	2 (3%)
Total time ICU in days (median, range)	2 (0 – 44)
Hospital stay in days (median, range)	19 (8 – 106)
In-hospital mortality	2 (3%)
Median follow-up surviving patients (months, range)	47 (12 – 104)
Recurrent disease	
Overall	30 (45%)
Locoregional	6 (9%)
Distant	14 (21%)
Both	10 (15%)
Death	
Total	41 (60%)
Tumor related	28 (41%)
Non-tumor related	12 (18%)
Unknown (no autopsy)	1 (2%)

ICU = Intensive Care Unit

Follow up and survival

After a median follow-up of 47 months in surviving patients, 27 patients (40%) were still alive (Table 2). Most deaths were tumor-related (n=28, 41%), but 12 patients (18%) died from non-tumor related causes. Recurrent disease was found in 30 patients (45%). The overall 5-year survival was 36% for all patients (Figure 1A). Several subgroup analyses were performed. There was no difference in overall survival between patients with an ASA score of I-II versus III-IV (34% vs 36%, p=0.869) (figure 1B). Patients who developed major postoperative complications (CDC ≥3) had a worse overall 5-year survival (29%) as compared to patients with no or minor complications (46%, p=0.020) (figure 1C).

Prognostic factors

To identify prognostic factors, analyses was conducted on all patients. For the development of any postoperative complication, A FEV1 <85% of the predicted value, BMI and age had a p<0.200 on univariable analysis. On multivariate analysis, none of them was significantly associated with the development of any postoperative complication (Table 3). Regarding the development of major complications (CDC ≥3); age was significantly associated on univariate analysis (p=0.027), whereas FEV1 <85% of the predicted value and BMI did not show a significant correlation, but had p<0.200. On multivariate analysis, age remained as the only independent prognostic factor (OR= 1.075, 95%CI=1.003 – 1.153, p=0.042).

Table 3 Multivariate analysis for identifying prognostic factors for postoperative morbidity and major complications (Clavien-Dindo grade ≥ 3).

Variables	Any postoperative complication			Major complication (CDC ≥ 3)		
	OR	**95% CI for OR**	**p-value**	**OR**	**95% CI for OR**	**p-value**
Age	1.042	0.982 – 1.105	0.173	1.075	1.003 – 1.153	0.042
FEV1 <85%	2.866	0.834 – 9.852	0.095	2.612	0.800 – 8.531	0.112
BMI	1.093	0.957 – 1.249	0.188	1.106	0.960 – 1.273	0.163

CDC = Clavien-Dindo Classification, OR = odds ratio, CI = confidence interval, FEV1 = forced expiratory volume in 1 second [% of predicted value].

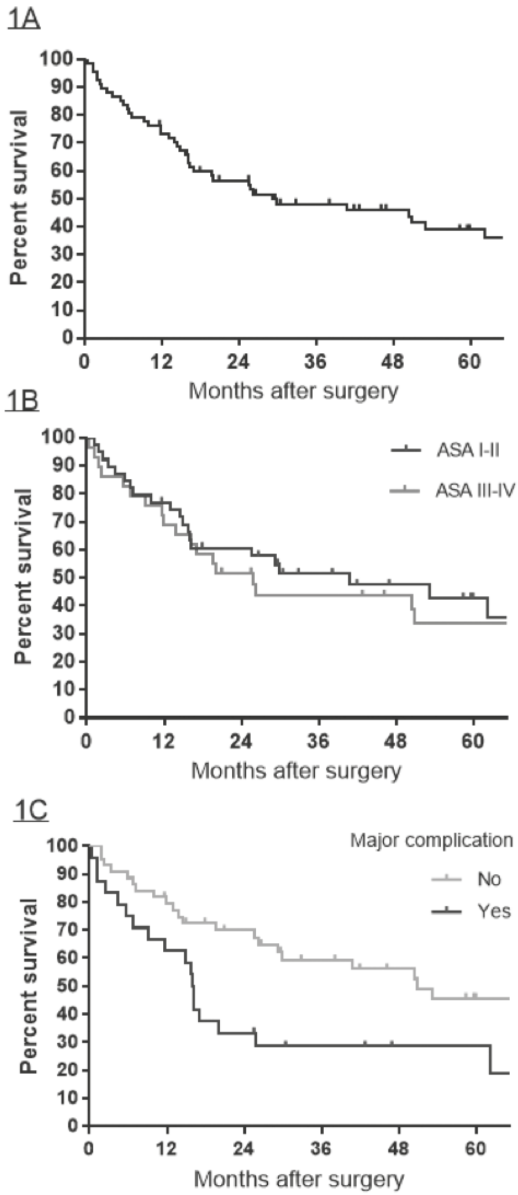

Figure 1 1A Overall survival in patients treated with a transhiatal esophagectomy. 1B survival depending on the American Society of Anaesthesiology (ASA) score; 1C survival depending on the development of major complications.

DISCUSSION

This study demonstrated that a THE for high-risk patients was accompanied with a high postoperative morbidity rate. Although 35% of these patients developed major complications requiring surgery or Intensive Care treatment, the in-hospital mortality rate was limited to 3% and a significant overall survival in these patients could be achieved. Thus, ASA score ≥ 3, severe pre-existing comorbidities and/or advanced age have an impact on postoperative outcomes following complex surgery such as THE. This study, however shows that these factors are no absolute contraindications. Most importantly, a 5-year survival rate of 36% reflects the benefit of taking the risk of this surgical procedure, even in this compromised group of patients.

A transthoracic esophagectomy (TTE) combined with a thorough mediastinal lymphadenectomy is considered to be the optimal treatment for locally advanced esophageal cancer[3], but is accompanied with a high postoperative morbidity rate[5, 8]. In addition, TTE is not feasible in patients with an elevated risk for surgery, since a thoracotomy might be too invasive. As reported by several studies, patients with an ASA-score >II, severe pre-existing comorbidities and advanced age are considered to be at risk for morbidity and mortality following TTE [7, 8, 11, 12]. At our institution, these patients are therefore treated with THE. Neoadjuvant treatment is not always administered in these patients, especially due to poor preoperative condition and comorbid disease. Despite the use of this less invasive approach and reduced rates of neoadjuvant therapy, a substantial number of these patients in our study developed postoperative complications.

After esophagectomy, a prognostic correlation between the presence of postoperative morbidity and overall survival has been demonstrated before[13, 14]. A recent study showed that the 5-year survival rates in patients with pStage 0, I and II disease who developed complications were significantly poorer than in those without complications (46% vs. 70%)[13]. Also in a large national cohort study, major postoperative complications were associated with impaired long-term survival[15]. In the current study, a worse overall survival was found in patients who developed major complications requiring surgery or ICU treatment. It has been hypothesized that major complications have a negative influence on patients' immune response, which could possibly enhance the development of residual microscopic disease to clinically manifest and fatal recurrent disease. On the other hand, it has also been hypothesised that patients with more advanced disease are more prone to develop complications because of a more compromised immune system and a higher load of unrecognized (micro) metastatic tumor that is left behind. Nevertheless, albeit a substantial part of the patients developed postoperative complications in the current study, a good 5-year survival of 36% could be achieved in these patients. Even so, it remains important to develop strategies to minimize postoperative morbidity which could improve outcomes after esophagectomy.

Anastomotic leakage was the most common complication following esophagectomy in this study and occurred in 35% of the high-risk patients. Most of them were manageable by opening the cervical wound, and only in 4 patients a reoperation was required consisting of mediastinal drainage or wash-out of thoracic empyema. Nevertheless, anastomotic leakage is associated with an increased risk of stricture formation and is an important cause of postoperative mortality and increased length of stay[16]. Several risk factors associated with anastomotic leakage have been identified, such as heart failure, renal insufficiency, vascular insufficiency and poor nutrition [16]. In the current study these factors were generally present in these patients. Furthermore, all patients were treated with a cervical anastomosis which is accompanied with a higher leakage rate as opposed to an intrathoracic anastomosis[16, 17]. An advantage of this technique, however, is the management of the leakage by opening the cervical wound as mentioned before. Nonetheless, this technique in this fragile group of patients resulted in a high anastomotic leakage rate compared to other series and it is therefore of the utmost importance to try and identify these patients preoperatively. We previously reported that atherosclerotic calcification of the aorta and right post celiac arteries that supply the gastric tube are independent risk factors for the development of anastomotic leakage after esophagectomy[18]. This can be used as an important factor in future prediction models to identify patients at high risk for leakage. In order to reduce the leakage rate, several studies investigated the use of ischemic conditioning of the stomach via arterial embolization or laparoscopic ligation before the planned esophagectomy[12]. Both techniques have been studied previously and showed a reduced rate of anastomotic leakage, but in a pooled analysis these rates were not significant[12]. It needs to be stressed that the included studies had some methodological concerns and furthermore, ischemic conditioning was applied in all patients. Future research with improved methodology and most importantly with application of these techniques in high-risk patients who may have actual benefit is justified for the evaluation of this technique.

Pneumonia was also a common complication in the present study, which occurred in 34% of patients. Following THE, pneumonia rates largely varies in the literature with rates reported between 2 – 30%[19, 20]. This wide range is probably due to variations in the definition of pneumonia. In some centers pneumonia was only recorded in case of a positive sputum culture whereas other studies defined pneumonia as any suspected infiltrate on a thoracic X-ray. In our study, we used the definition of the revised Uniform Pneumonia Score (rUPS) which included temperature, leukocyte count and pulmonary radiography[21]. An international standardized definition of perioperative complications is required to harmonize complication rates and to facilitate future comparative studies. Pneumonia has been significantly associated with the need for re-intubation, prolonged hospital stays and hospital mortality [22, 23]. To reduce the rate of pulmonary complications, some studies on preoperative optimization of the performance status through inspiratory muscle training and adequate enteral nutrition showed promising results[24, 25]. Further research will provide more evidence on the effectiveness of these strategies [26].

Several risk scores have identified the importance of premorbid cardiac, respiratory and renal disease in predicting adverse outcomes following esophagectomy [8, 27]. In this study, only age was found to be the only independent prognostic factor associated with the development of major postoperative complications. It has been demonstrated before by a systematic review that increasing age had a significant impact on outcomes following esophagectomy, especially on cardiac and pulmonary complications along with increased in-hospital mortality and discharge disposition[12]. It is not surprising that elderly patients are at higher risk for postoperative morbidity and mortality, since they generally have more major comorbidities that may complicate surgery, such as a decreased capacity to adapt to stress, cardiovascular and pulmonary disease, greater functional impairment and physical disability and diminished cognitive function. It is important to identify these patients as a high-risk cohort so that they can be carefully risk-stratified, counselled and selected for surgery. Furthermore, they could receive intense pulmonary rehabilitation to strengthen their respiratory muscles before surgery [26]. This may reduce chances of postoperative pulmonary complications.

In conclusion, the selective use of transhiatal esophagectomy for high-risk patients resulted in a good 5-year survival even though the minority of the patients was treated with neoadjuvant therapy. Post-operative complications do occur in a high number of these frail patients, but most are manageable and this results in a low mortality rate.

Hence, the selective use of a transhiatal approach offers a chance for cure in patients with an elevated risk for esophagectomy. Particularly older patients could benefit from pre- and postoperative medical optimization, since they have an increased risk of developing postoperative complications.

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Chapter 7

Current status of laparoscopic transhiatal esophagectomy for esophageal cancer patients: a systematic review of the literature.

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Diseases of the Esophagus,
2016 Feb 26; [Epub ahead of print]

ABSTRACT

Background

Minimally invasive techniques in transhiatal esophagectomy (THE) were introduced in order to reduce morbidity and enhance postoperative recovery. Aim of this study was to systematically review the current status and possible beneficial effects of the minimally invasive approach in THE.

Methods

A systematic search was performed in PubMed, the Cochrane Library and Embase to identify English articles published on laparoscopic THE. Comparative cohort studies were included for critical appraisal. Data describing perioperative and oncological outcomes were analysed.

Results

A total of 4 comparative cohort studies that compared laparoscopic THE (n=122) with open THE (n=144) and 4 non-comparative cohort studies reporting on laparoscopic THE (n=212) were included in this review. Median blood loss was significantly lower in the laparoscopic group in all studies (100 – 500 vs 526 – 900 ml). Length of hospital stay was also significantly shorter for a laparoscopic approach in all studies (9 – 13 vs 12 – 16 days). One study reported less major postoperative complications after laparoscopic THE (12 vs 23%), in the other studies no differences were found. Also no differences were found in regard to operating time, morbidity, radicality and lymph node retrieval.

Conclusion

Based on these pioneer studies, laparoscopic THE was demonstrated to be safe and feasible with evidence of reduced blood loss and shorter hospital stays. However, level 1 evidence is lacking and further research is warranted to confirm these findings and also to evaluate long-term oncologic outcomes.

INTRODUCTION

Esophagectomy is the key element in the curative treatment of patients with esophageal cancer. However, the type of approach and extent of lymphadenectomy that is necessary for esophageal cancer patients remains controversial[1,2]. Transthoracic esophagectomy (TTE), is advocated because of its extended mediastinal lymph node dissection and improved locoregional control[3,4]. Others have advocated the transhiatal esophagectomy (THE) for distal esophageal cancer offering decreased postoperative morbidity with supposedly no compromise in cancer recurrence or survival[5]. Regardless of the type of approach, both procedures still have high complication rates, varying between 40 to 80%[6]. This has encouraged the search for alternative techniques that achieves similar oncological outcomes but with less morbidity and faster recovery times. With this objective in mind, minimally invasive techniques in esophagectomy were introduced for TTE by Cushieri and colleagues[7] in 1992 and for THE by dePaula and colleagues[8] in 1995. A recent meta-analysis showed that minimally invasive esophagectomy (MIE) reduces overall morbidity and pulmonary complications and could lead to a shorter hospital stay[9]. This was, however, only reported for the transthoracic approach. By avoiding a thoracotomy, it seems obvious that pulmonary complications can be reduced. However, in a laparoscopic approach these benefits are less obvious. To date, no systematic review or meta-analysis has been reported comparing laparoscopic versus open transhiatal esophagectomy. Hence, this systematic review was conducted in order to elucidate the current status and possible beneficial effect of the minimally invasive approach in transhiatal esophagectomy.

PATIENTS AND METHODS

The present review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10].

Search strategy

A systematic search was performed in PubMed, the Cochrane Library and Embase (January 1985 – January 2015). The search included three different domains and the medical subject headings (MeSH) terms and keywords between the domains were combined with ‘AND’. Within the domains, the terms were combined with ‘OR’. The first domain contained terms related to ‘esophagus’ and ‘gastro-esophageal junction’, the second domain contained terms related to ‘cancer’, and the third domain contained terms related to treatment (i.e. open or laparoscopic transhiatal esophagectomy). The terms were restricted to title and abstract. A full description of the search strategy is available in Appendix S1 (supporting information). Only original studies on humans and written in English were considered for inclusion. Duplicate publications were excluded. To enhance the search sensitivity, a manual hand-search was performed using cross referencing of included studies. The last search was performed on 17 October 2015.

Study selection

All eligible studies were retrieved and studies that seemed unrelated to the study aims were excluded based on single author title review. For the remaining studies all abstracts were independently assessed for eligibility by two authors (KP and JR). Full papers were retrieved for all abstracts deemed potentially eligible. Full papers underwent dual author review and were assessed against inclusion/exclusion criteria. In case of discrepancies between the two authors regarding eligibility, a consensus was reached through discussion.

Inclusion and exclusion criteria

Primary endpoints included were morbidity and duration of hospital stay. Secondary endpoints were blood loss, duration of the surgical procedure and oncological outcomes (resection margin and lymph node retrieval). Reporting of at least one of these outcomes for laparoscopic THE was considered sufficient for inclusion. Comparative cohort studies between laparoscopic and open THE were included if they had a sample size > 10 per treatment group. Studies were excluded if they were review articles, meta-analyses, experimental studies or non-comparative cohort studies with a sample size ≤ 30. In case of duplicate publications reported by the same author with overlapping or similar patient outcomes, only the study with the best quality or the most complete data was considered.

Quality assessment

The methodological quality of the included comparative studies were critically appraised according to the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence[11]. The risk of bias was assessed using a standardized list of ten potential risk factors of bias, based on the Oxford CEBM Critical Appraisal Skills Programme appraisal sheet for observational cohort studies[12, 13].

Statistical analysis

Outcomes were expressed as reported originally. Due to the heterogeneity between the studies, no formal meta-analysis could be performed. Some studies reported medians with range and some studies reported means with standard deviation. It was therefore not possible to calculate weighted means.

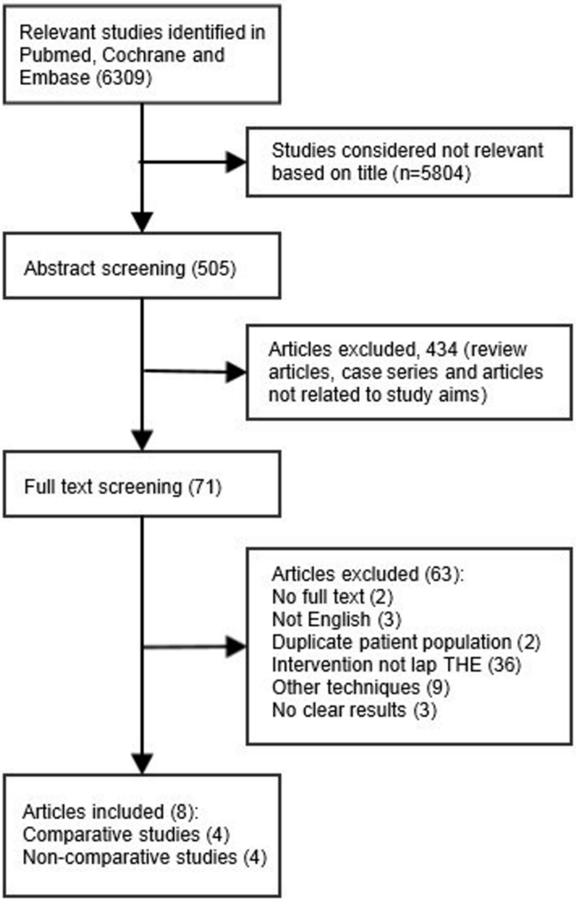

Figure 1 Flowchart of the search strategy. Lap THE = laparoscopic transhiatal esophagectomy.

RESULTS

Eligible studies

A flowchart of the literature search process is shown in Figure 1. The initial search identified 6309 unique records from the electronic databases. Of these, 5804 records were excluded after initial screening of titles and another 434 records were excluded after screening of abstracts. In total 71 articles were included for full-text review, after which 63 were excluded based on no full text available, not written in English, reporting of duplicate patient populations, intervention was not laparoscopic THE, usage of novel techniques in THE or poorly reported results. In total 8 studies remained available for analysis, of which 4 were comparative cohort studies[14-17] and 4 were non-comparative cohort studies[18-21]. The results of the critical appraisal to assess the methodological quality of the comparative studies are shown in Table 1. None of the included studies performed a prospective calculation of the sample size nor were patients randomized. The level of evidence for the studies ranges between 3 – 4. Baseline characteristics of the included studies are outlined in table 2. In total 266 patients were involved in the comparative studies, of which 122 underwent laparoscopic and 145 open THE. Mean age ranged between 61 – 76 years. In one study[15], patients treated with the laparoscopic approach were significantly older (69 vs 61y, p=0.003) with a lower BMI (28 vs 32, p=0.030). In another study[17], the male gender percentage was significantly higher in the open group (85 vs 67%, p=0.003).

Outcome parameters

Postoperative complications

The overall morbidity for the laparoscopic treated patients ranged between 9 – 62% with reoperation rates varying between 0 – 10% (table 3). In the comparative studies, the overall morbidity rate was reported in 3 studies[15-17]. In those studies, the morbidity rate decreased with 20% for the laparoscopic approach, however this was not significant in any of the studies. In two studies, the morbidity was further specified as minor and major complications[15, 17]. Minor complications were those that did not require any interventional procedures or reoperations. There were no differences between laparoscopic and open THE regarding minor complications, however in the study by Cash and colleagues[17], major complications occurred more often in the open group (12 vs 23%, p=0.04). The reoperation rate was reported in 2 studies and this did not differ between both techniques[16, 17].

Table 1 Critical appraisal of the included studies reporting on open versus laparoscopic transhiatal esophagectomy.

Reference	Level of evidence*	Study design	Clear inclusion and exclusion criteria	Similar groups	Standardized treatment	Same follow-up and data collection	Missing data verified	Analysis	Risk of selection bias	Measurement bias	Confounding factor
Bernabe et al. (2005)	4	Retrospective	+	+	+	n.a.	n.r.	+	+	+	+
Perry et al. (2009)	3	Retrospective	+	–	±	+	n.r.	+	+	+	+
Maas et al. (2012)	3	Retrospective	+	+	–	+	n.r.	+	+	+	+
Cash et al. (2013)	3	Retrospective	+	–	–	–	n.r.	+	+	+	+

Pulmonary complications

Patients treated with the laparoscopic approach developed pulmonary complications in 15 – 24% (table 3). These included pneumonia, pneumothorax, pleural effusion and acute respiratory distress syndrome. In the comparative studies, pulmonary complications were reported in 2 studies and in both studies no difference was found between both techniques[15, 16]. In the first study[15], pulmonary complications occurred in 24% of the laparoscopic and 29% of the open group, while in the other study[16], this was 18% for laparoscopic and 26% for open THE.

Anastomotic leakage

The anastomotic leakage rate ranged between 3 and 25% for laparoscopic treated patients (table 3). Only two comparative studies reported on anastomotic leakage and in both studies no significant differences were found[15, 17]. In the study by Perry and colleagues[15] anastomotic leakage was found in 19% of the patients treated laparoscopically versus 29% in the open group. In the study by Cash and colleagues[17] this was respectively 9% versus 13%.

ICU and hospital stay

Median ICU stay ranged between 1 – 3 days for patients treated with the laparoscopic approach (table 3). Two comparative studies reported on ICU stay and in the study by Maas and colleagues[16] this was significantly shorter for the laparoscopic group (1 vs 3 days, p<0.001). In the study by Perry and colleagues[15], also a shorter ICU stay for the laparoscopic group was found, however not significantly (2 vs 3 days, p=0.150). Regarding the length of hospital stay, 7 – 13 days were reported for laparoscopic treated patients. In all of the comparative studies, the median length of hospital stay was significantly shorter for the laparoscopic group (9 – 13 vs 12 – 16 days). The difference in hospital stay between the laparoscopic and open approach ranged between 2 – 4 days.

Table 2 Baseline characteristics of the includes studies

	Study	Study design	Approach	Sample size	Gender (M/F)	Age (median, range)
Comparative cohorts	Bernabe et al. (2005)	Retrospective	LTH	17	16/1	64 ± 14†
			OTH	14	11/3	64 ± 10†
	Perry et al. (2009)	Retrospective	LIE	21	18/3	69 ± 8†
			OTH	21	17/21	61 ± 9†
	Maas et al. (2012)	Retrospective	LTH	50	41/9	63 (57-69)
			OTH	50	33/17	65 (57-69)
	Cash et al. (2013)	Retrospective	LTH	33	22/11	72 (50-83)
			OTH	60	51/9	76 (70-80)
Non-comparative cohorts	Palanivelu et al. (2007)	Prospective	LTH	32	22/10	62 (39-72)
	Tinoco et al. (2007)	Retrospective	LTH	68	50/18	56 (28-73)
	Montenovo et al. (2011)	Retrospective	LTH	72	58/14	64 (42-83)
	Dunn et al. (2013)	Retrospective	RATH	40	32/8	65 (36-84)

†mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH =robot-assisted transhiatal esophagectomy, NR = Not reported.

Operating time

The median operating time for laparoscopic THE ranged between 200 – 399 minutes (table 4). There were no differences found between the laparoscopic and the open group. Bernabe and colleagues[14] reported a sub analysis of the last 6 laparoscopic vs 6 open THE and found a shorter operating time for the laparoscopic approach (311 vs 388 minutes, p=0.010).

Blood loss

Median blood loss ranged between 100 – 500 mL for laparoscopic treated patients (table 4). In all of the comparative studies that reported on blood loss, the laparoscopic approach had significantly less compared to the open approach. In the open groups, median blood loss ranged from 526 to 900 mL. One study did not mention blood loss, but instead reported on the necessity of perioperative blood transfusion[17]. This was significantly lower for the laparoscopic group at 0, compared with 2.5 in the open group.

Oncological outcomes

Radical resection margins for the laparoscopic approach ranged between 82 – 100% (table 4). Two comparative studies reported on the resection margins and had comparable rates for both techniques[15,16]. The number of removed lymph nodes ranged between 3 – 24 for the laparoscopic approach. In the comparative studies, the numbers varied between the studies. In two studies, no differences were found between the laparoscopic and open technique[14, 16]. However, in one study the number of resected lymph nodes was significantly lower for the laparoscopic group (24 vs 36, p<0.001)[17], whereas in another study this was significantly higher for the laparoscopic group (10 vs 3, p=0.005)[15]. Only two studies reported survival data and in both studies no significant differences were found. In the study by Maas and colleagues[16], the 5-year survival was laparoscopic and open THE was respectively, 29% vs 26%. In the study by Cash and colleagues[17], 2-year survival was 70% for laparoscopic and 65% for open THE.

Table 3 Postoperative course

	Study	Approach	Morbidity	Pulmonary	Anastomotic leakage
Comparative cohorts	Bernabe et al. (2005)	LTH (n=17)	NR	NR	NR
		OTH (n=14)	NR	NR	NR
	Perry et al. (2009)	LIE (n=21)	13 (62%)	5 (24%)	4 (19%)
		OTH (n=21)	17 (81%)	6 (29%)	6 (29%)
	Maas et al. (2012)	LTH (n=50)	21 (42%)	9 (18%)	NR
		OTH (n=50)	33 (66%)	13 (26%)	NR
	Cash et al. (2013)	LTH (n=33)	13 (39%)	NR	3 (9%)
		OTH (n=60)	37 (61%)	NR	8 (13%)
Non-comparative cohorts	Palanivelu et al. (2007)	LTH (n=32)	3 (9%)	NR	1 (3%)
	Tinoco et al. (2007)	LTH (n=68)	32 (47%)	13 (19%)	10 (15%)
	Montenovo et al. (2011)	LTH (n=72)	37 (51%)	11 (15%)	14 (19%)
	Dunn et al. (2013)	RATH (n=40)	NR	8 (20%)	10 (25%)

†mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, NR = Not reported

Table 4 Perioperative outcomes

	Study	Approach	Operating time in minutes (median, range)	Blood loss mL (median, range)
Comparative cohorts	Bernabe et al. (2005)	LTH (n=17)	336 ± 102†	331 ± 220†
		OTH (n=14)	388 ± 53†	542 ± 212†
	Perry et al. (2009)	LIE (n=21)	399 ± 86†	168 ± 149†
		OTH (n=21)	408 ± 127†	526 ± 289†
	Maas et al. (2012)	LTH (n=50)	300 (265-320)	500 (400-650)
		OTH (n=50)	280 (250-320)	900 (650-1400)
	Cash et al. (2013)	LTH (n=33)	274	NR
		OTH (n=60)	276	NR
Non-comparative cohorts	Palanivelu et al. (2007)	LTH (n=32)	200 (180-310)	150 (50-700)
	Tinoco et al. (2007)	LTH (n=68)	153 (lap component)	NR
	Montenovo et al. (2011)	LTH (n=72)	299 (212-700)	300 (75-1700)
	Dunn et al. (2013)	RATH (n=40)	311 (226-491)	100 (25-300)

†mean ± standard deviation, LTH = laparoscopic transhiatal esophagectomy, OTH = open transhiatal esophagectomy, NR = Not reported.

Re-operation	ICU stay (median, range)	Hospital stay (median, range)	In hospital mortality
NR	NR	9 ± 3†	0
NR	NR	12 ± 3†	0
NR	2 (2-4)	10 (8-14)	0
NR	3 (2-10)	14 (10-19)	1 (5%)
2 (4%)	1 (1-2)	13 (11-16)	0
3 (6%)	3 (2-4)	16 (14-20)	1 (2%)
0	NR	10	0
6 (10%)	NR	13	1 (2%)
NR	1 (1-28)	7 (5-42)	0
NR	NR	7	4 (6%)
2 (3%)	1 (1-35)	9 (7-58)	1 (1%)
0	1 (0-21)	9 (6-36)	1 (3%)

esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH =robot-assisted transhiatal

Conversion	Lymph nodes (median, range)	Radical resection	Stage
0	9	NR	0-I
	10	NR	0-I
0	10 (4-12)	21 (100%)	0-II
	3 (0-7)	21 (100%)	0-II
9 (18%)	14 (10-19)	41 (82%)	I-III
	11 (8-15)	37 (74%)	I-III
2 (6%)	24	NR	I-III
	36	NR	I-III
0	15 (9-32)	32 (100%)	I-III
5 (7%)	NR	NR	I-IV
0	11 (2-32)	72 (100%)	I-III
5 (12.5%)	20 (3-38)	37 (95%)	0-IV

esophagectomy, LIE = laparoscopic inversion esophagectomy, RATH = robot-assisted transhiatal

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DISCUSSION

This is the first systematic review evaluating laparoscopic versus open transhiatal esophagectomy. Thus far, no randomized controlled trial evaluating these techniques has been conducted and after a literature search, only 4 comparative cohort studies were identified. Based on these pioneer studies, it was demonstrated that laparoscopic THE is a safe and feasible alternative to the open approach, with evidence of reduced blood loss and a shorter hospital stay. The laparoscopic approach may also decrease short-term morbidity with comparable operating times and oncological outcomes. Long term overall survival data were not yet reported adequately.

Minimal invasive techniques in esophageal surgery were introduced to decrease postoperative morbidity by reducing the surgical trauma. In the current review, three studies reported on overall morbidity and demonstrated a decrease of 20% in patients treated with a laparoscopic approach. However in all of these studies the difference was not significant[15-17]. Only one study reported significantly less major complications that required an intervention or reoperation in the laparoscopic group[17]. Regarding pulmonary complications and anastomotic leakage, also no differences were observed. In TTE, the benefit of a MI approach in reducing morbidity was evident since there was a 50% decrease in total morbidity and significantly fewer pulmonary complications in the MI approach[9, 22]. In THE, the supposed differences might be smaller because of the avoidance of a thoracic phase. In addition, all comparative studies in this review were relatively small, i.e. the largest laparoscopic cohort included 50 patients which makes it difficult to gain significant power. Also, the results may reflect the early experience of the authors with this technique. The overall morbidity rate for the laparoscopic approach ranged from 9 to 61% and is comparable to large open THE series[5, 23-25]. This wide range is probably due to variations in the definition of complications. For example, in some centers pulmonary complications were defined as any unexpected pulmonary event (atelectasis, pleural effusion etc.) whereas in other centers only the most severe pulmonary complications were addressed (ARDS, need for tracheostoma).

Although differences in morbidity rates between the laparoscopic and open approach were not significant, all comparative studies reported a significantly shorter hospital stay for the laparoscopic approach, with differences ranging between 2 – 4 days. This advantage of minimal invasive techniques regarding postoperative recovery was demonstrated before in the transthoracic approach. In a recent meta-analysis, the ICU and hospital stay were both significantly reduced if patients were treated with MIE as compared to the standard open transthoracic approach[9]. In the only randomized controlled trial reported thus far, the hospital stay significantly decreased from 14 days in the open transthoracic group to 11 days in the MIE group[22]. The decreased hospital stay for the MI techniques in both TTE and THE may be related to the reduced operative trauma and subsequently reduced inflammation which allows for a more adequate pain control and improved patient mobilization, and thereby facilitating recovery. This highlights the advantage of the minimally invasive approach in THE.

The laparoscopic technique had raised some concerns regarding oncological outcomes. At first glance, there were no differences between resection margins and lymph node retrieval between laparoscopic and open THE. However, it needs to be stressed that the number of studies was small, one study only included limited disease, three studies also included Stage 0 disease, and not all studies reported on these outcomes. It is therefore not possible to draw any conclusions from these studies, and the short-term oncological outcomes should be interpreted with caution. Also regarding the long-term oncological outcome, results were inadequately documented. A recent meta-analysis[26] that had focused purely on the oncological merits of MIE techniques versus conventional open esophagectomy demonstrated that MIE provides for a more complete lymph node clearance as compared to the open approach (16 vs 10, p=0.03) with no differences in regard to tumor stage. Also comparable survival rates were reported, which has showed that MIE is equivalent to standard open esophagectomy in achieving similar oncological outcomes. However, the studies is this meta-analysis were all comparative cohort studies and most of the included patients were treated via the transthoracic approach. Further research is needed to provide evidence of similar oncological results between laparoscopic and open THE.

Several limitations of the current systematic review must be taken into account when considering its results. First, the overall quality of the comparative studies is moderate. All studies were nonrandomized, nonblinded, comparative cohort studies or case-control studies with a limited number of patients, which inevitably introduces selection bias. To provide a reliable indication of the quality of the included studies, a critical appraisal was performed and CEBM levels were assigned. Second, there was a variation in inclusion criteria between the studies including limited disease, operative technique, and variations in the reporting on outcomes. Due to the obvious heterogeneity between the studies we could not perform a formal meta-analysis.

Finally, the sample size in the studies were relatively small and it was not clear whether the laparoscopic treated patients resembled the author's first experience with this technique. It is not completely elucidated what a reasonable learning curve is in laparoscopic THE. In transthoracic MIE and laparoscopic total gastrectomy some studies reported improved operative and perioperative parameters after 35 – 40 patients[27, 28]. Hence, the results of the included studies in the current systematic review may reflect the adaptation phase of the laparoscopic approach. In order to overcome the limitations of the included studies and to provide for a higher level of evidence, a prospective randomized controlled trial is warranted. However, there are several challenges in setting up such a trial including learning curve, credentialing of surgeons and standardization of coding of complications. Preferably, this trial should be set up in high-volume Upper-GI centers with surgeons experienced in both laparoscopic and open THE and with an experienced multi-disciplinary team for the postoperative care. The primary focus of the trial should be on reducing the hospital stay and postoperative morbidity with laparoscopic THE.

In conclusion, results from pioneer comparative cohort studies showed that a laparoscopic approach for transhiatal esophagectomy is a feasible and safe alternative to the open approach. The laparoscopic approach leads to reduced perioperative blood loss and a shorter hospital stay. Furthermore, laparoscopic THE may lead to decreased short-term morbidity. However, evidence is lacking and further research, preferably a prospective randomized controlled trial, is warranted to confirm these findings and also to evaluate long-term oncologic outcomes.

SUPPLEMENTARY FILE

1. Search strategy

Domain 1:
("esophageal"[Title/Abstract]) OR "oesophageal"[Title/Abstract]) OR "esophagus"[Title/Abstract]) OR "oesophagus"[Title/Abstract]) OR "gastro esophageal"[Title/Abstract]) OR "gastro oesophageal"[Title/Abstract]) OR "gastroesophageal"[Title/Abstract]) OR "gastrooesophageal"[Title/Abstract]) OR "esophagogastric"[Title/Abstract]) OR "oesophagogastric"[Title/Abstract]) OR "cardia"[Title/Abstract]) OR "oesogastric"[Title/Abstract]) OR "gej"[Title/Abstract]) OR "egj"[Title/Abstract])

AND

Domain 2:
("cancer"[Title/Abstract]) OR "cancers"[Title/Abstract]) OR "tumor"[Title/Abstract]) OR "tumours"[Title/Abstract]) OR "tumour"[Title/Abstract]) OR "neoplasm"[Title/Abstract]) OR "neoplasms"[Title/Abstract]) OR "malignancy"[Title/Abstract]) OR "malignancies"[Title/Abstract]) OR "adenocarcinoma"[Title/Abstract]) OR "adenocarcinomas"[Title/Abstract]) OR "carcinoma"[Title/Abstract]) OR "carcinomas"[Title/Abstract]) OR "squamous cell"[Title/Abstract])

AND

Domain 3:
("video assisted"[Title/Abstract]) OR "minimally invasive"[Title/Abstract]) OR "minimal invasive"[Title/Abstract]) OR "laparoscopic"[Title/Abstract]) OR "transhiatal"[Title/Abstract]) OR "esophagectomy"[Title/Abstract]) OR "oesophagectomy"[Title/Abstract]) OR "laparoscopy"[Title/Abstract]) OR "esophageal resection"[Title/Abstract]) OR "oesophageal resection"[Title/Abstract]) OR "esophagus resection"[Title/Abstract]) OR "oesophagus resection"[Title/Abstract]) OR "esophagectomies"[Title/Abstract]) OR "oesophagectomies"[Title/Abstract]) OR "mie"[Title/Abstract]) OR "laparotomy"[Title/Abstract])

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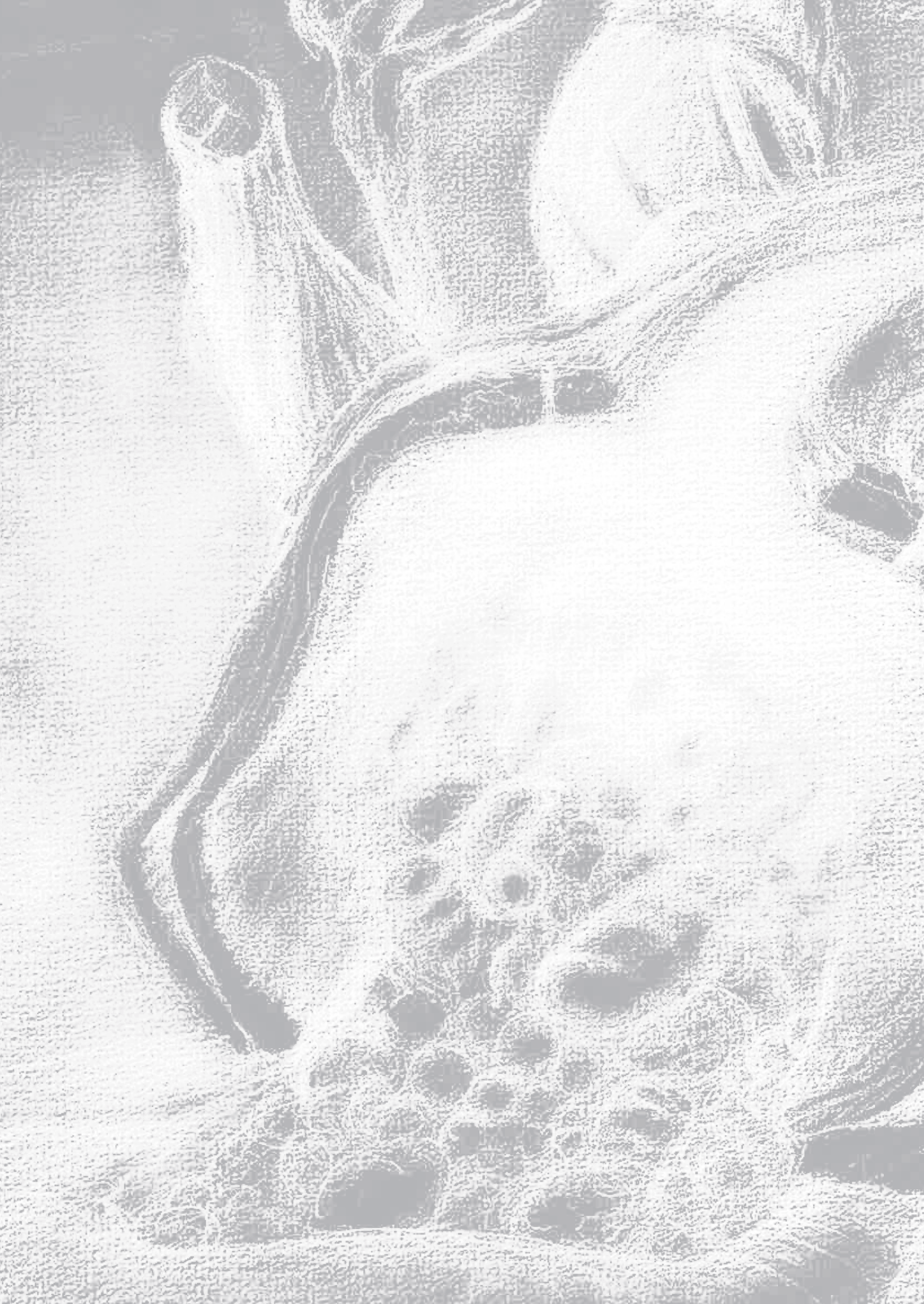
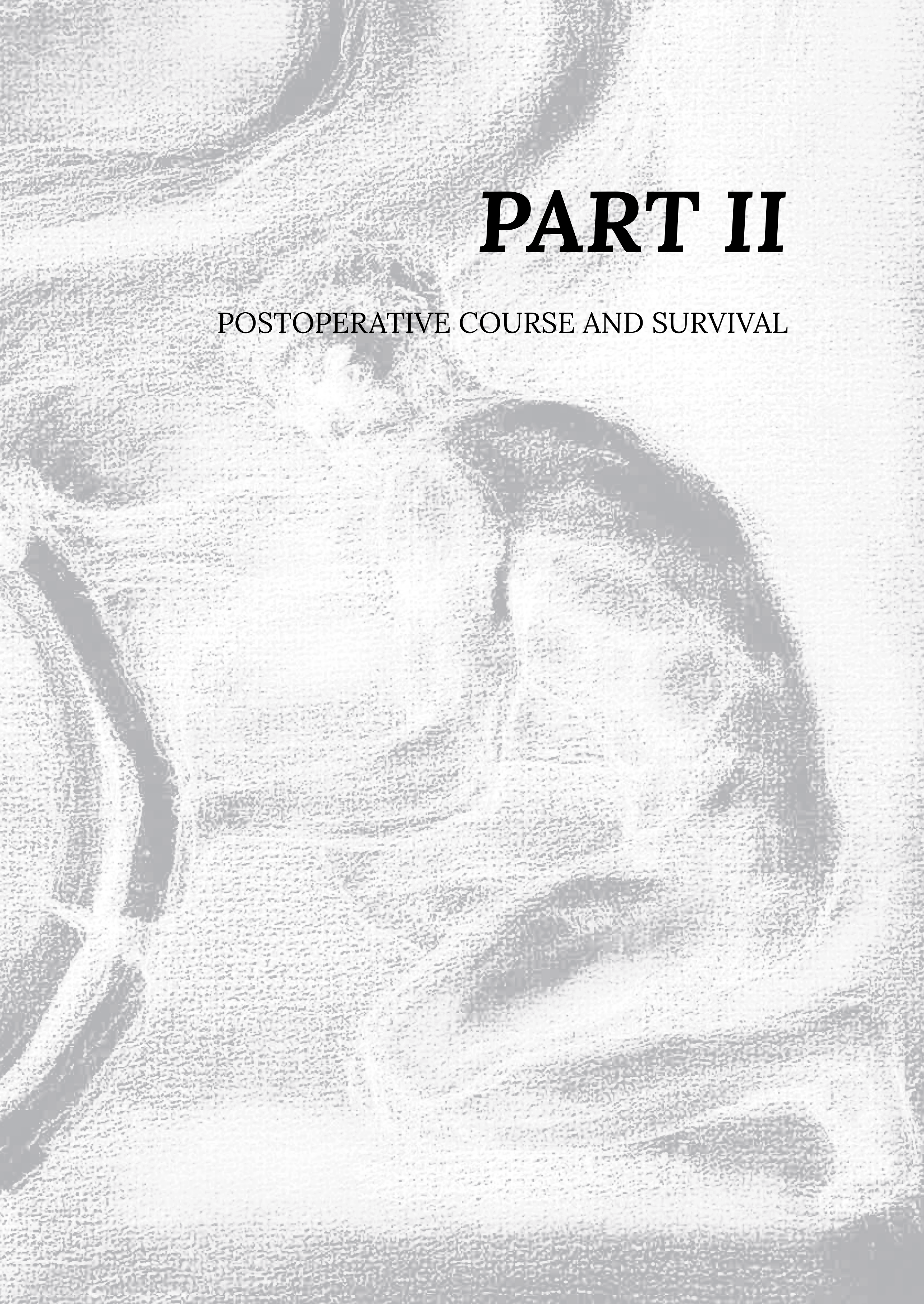


PART II

POSTOPERATIVE COURSE AND SURVIVAL



Chapter 8

Intermittent pneumatic compression in combination with low-molecular weight heparin in the prevention of venous thromboembolic events in esophageal cancer surgery.

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Journal of Surgical Oncology, [in press]

ABSTRACT

Background

Aim of this study was to evaluate the use of Intermittent Pneumatic Compression (IPC) in the prevention of symptomatic venous thromboembolic events (VTE) in patients undergoing esophagectomy for cancer.

Methods

From a prospective database, all patients operated between 2010-2014 received IPC in addition to LMWH and were compared to a historical cohort of patients treated LMWH only (2004-2009).

Results

Of the 313 included patients, 195 (62%) received IPC. Patients with IPC received neoadjuvant chemoradiation more often (45% vs 3%, $p<0.001$), whereas neoadjuvant chemotherapy was equally distributed (31% vs 34%, $p=0.631$). There were no differences with regard to surgical approach, operative time, blood loss and ICU stay. Patients treated without IPC had a longer hospital stay (18 vs 15 days, $p=0.014$). Overall, 12 clinical VTE's occurred in 11 patients, which consisted of 2 deep venous thromboses and 10 pulmonary embolisms. In the group of patients who received IPC 1.5% developed a symptomatic VTE compared to 6.8% in patients without IPC (OR=0.215; 95% CI=0.06-0.83). Multivariate analysis identified IPC as the only independent prognostic factor correlated with a reduction in postoperative VTE's (OR=0.225; 95% CI=0.06-0.88).

Conclusion

The addition of IPC in patients undergoing esophagectomy was associated with a reduction in symptomatic VTE's.

INTRODUCTION

Venous thromboembolic events (VTE), consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), are common complications in cancer patients undergoing surgery and even the most common cause of death during the first 30 postoperative days [1–3]. There are many factors associated with the development of VTE in cancer patients such as cancer-related factors (primary site, stage, histology), treatment-related factors (major surgery, chemotherapy, transfusions) and patient-related factors (age, race, comorbidities)[4]. Therefore, the risk of venous thrombosis varies between different types of cancer and is especially high among patients undergoing esophageal cancer surgery. These patients are often elderly with advanced tumors, have several comorbidities and are exposed to long immobilization during surgery and during the immediate postoperative period. Hence, VTE rates up to 13.2% following esophagectomy have been reported [2, 5, 6].

The postoperative incidence of VTE can be reduced through the use of prophylactic measures, which includes low-molecular weight heparin (LMWH), compression stockings and early postoperative mobilization. In the latest version of the guideline by the American College of Chest Physicians (ACCP), LMWH has been recommended as the standard prophylactic anticoagulant in patients undergoing thoracic surgery, including esophagectomy[7]. In addition to these measures, the use of specific mechanical prophylaxis including Intermittent Pneumatic Compression (IPC) has been shown to be effective in various surgical procedures such as gastro-intestinal, orthopaedic, cardiac and neurosurgical surgery [8-11]. low molecular weight heparin-LMWH and early mobilization, a retrospective study in cranial neurosurgery using intraoperative MRI was performed.

PATIENTS AND METHODS

Study population

Between January 2006 and May 2014 a total of 332 consecutive patients underwent esophagectomy with gastric tube reconstruction at the University Medical Center Utrecht. These patients were recorded in a prospective database. All patients were diagnosed with a clinical resectable tumor (cT1a-T4a) without evidence of metastatic disease (cM0) according to the seventh edition of the IPCC TNM staging system[12].

Treatment approach

Patients were pre-treated with neoadjuvant chemo(radio)therapy if they had locally advanced tumors (≥T2) or with N+ disease. Before June 2012, eligible patients were treated with neoadjuvant chemotherapy, which consisted of 3 cycles of epirubicin, cisplatin and 5-fluorouracil preoperatively and 3 cycles postoperatively. After that, eligible patients were treated with neoadjuvant chemoradiotherapy, which consisted of 5 preoperative cycles of carboplatin and paclitaxel and concurrent radiotherapy (41.1Gy). Before 2008 chemotherapy was not yet incorporated in the standard treatment protocol and not all patients had received chemotherapy. Other reasons for not commencing chemo(radio)therapy were the following: WHO performance status ≥2, weight loss >10% or patient request. Surgery was performed by either open or laparoscopic esophagectomy followed by gastric tube reconstruction and left-sided cervical anastomosis and was generally scheduled within 3-9 weeks after completion of the last preoperative cycle.

Thromboembolic prophylaxis

Between January 2006 and January 2010 all patients received LMWH (dalteparin 5000 units daily subcutaneously) starting on the day of surgery (preoperatively) during discharge from hospital according to local protocol (Group 1, figure 1). In January 2010 the IPC-system (Kendall SCD^{tm} Sequential Compression System, Covidien, Germany) was introduced at our institution. Between January 2010 and July 2010, only one IPC-device was available and it is not clear if all patients received IPC in this time period (n=19). These patients were excluded from the initial analyses. A sensitivity analysis was also conducted to demonstrate possible differences in case these patients were

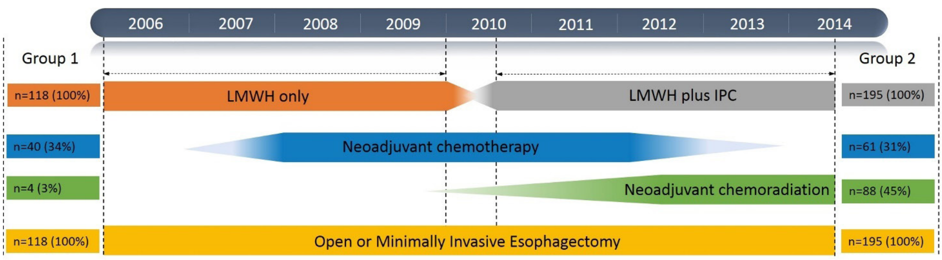

Figure 1 Timeline of the treatment approach regarding neoadjuvant therapy and surgery in group of patients treated with low-molecular weight heparin (LMWH) alone (Group 1) and patients treated with LMWH plus Intermittent Pneumatic Compression (IPC, group 2).

included in the IPC-group. In July 2010 IPC became standard of care and all patients received this device additionally to conventional thromboprophylaxis with LMWH (Group 2). On arrival in the operating room, the IPC stocking was placed on both legs and connected to the compressor device for the entire procedure. Patients continuously received IPC until discharge of the Intensive Care Unit (ICU). The group of patients who received IPC with conventional LMWH (Group 2) were compared to the group of patients receiving conventional LMWH alone (Group 1). Figure 1 maps out the treatment approach in both groups regarding neoadjuvant therapy and surgery throughout the time.

Postoperative course

A postoperative venous thromboembolism was defined as the occurrence of clinically detected deep venous thrombosis (DVT) or pulmonary embolus (PE). All events that occurred within 30 days after surgery or during the postoperative in-hospital stay were taken into account. Patients were only screened for DVT or PE if clinically suspected, therefore only symptomatic VTE's were taken into account. Diagnosis was confirmed by Doppler ultrasonography of the leg for DVT and a CT pulmonary angiography for PE. D-dimer or any other fibrin-related markers were not used for diagnosis. VTE's and all other postoperative complications were scored weekly during a plenary consensus meeting and prospectively collected in our database.

Statistical analysis

Differences between patients treated with and without IPC were evaluated by means of the Mann-Whitney U (MWU) test for continuous variables and the Pearson's Chi-squared (χ^2 test) – or Fisher's exact test in case of small cell count – for categorical variables. Univariate logistic regression analyses were conducted to identify factors affecting the development of postoperative VTE's. Since the continuous variables (age, Body Mass Index (BMI), operative time and length of stay) were not equally distributed (assessed with the Shapiro Wilk test) both the unadjusted data and adjusted log data were used for analysis. All factors with a p-value < 0.150 on univariate analysis were entered in a multivariate logistic regression model using the Enter-method. A p-value < 0.05 was considered statistically significant. IBM SPSS Statistics (version 21; IBM Corporation, Armonk, NY) was used to conduct all analyses.

RESULTS

Study population and histopathological characteristics

A total of 313 consecutive patients with cancer of the esophagus or esophagogastric junction (EGJ) underwent esophagectomy during the study period. Data was complete in all patients. Of these, 195 received (62%) IPC intra- and postoperatively in addition to conventional LMWH. The remaining 118 patients (38%) were treated with conventional LMWH alone. Median age was 65 years (range 38 - 84) (Table 1). There were no significant differences with respect to age, gender, BMI, American Society of

Table 1 Baseline characteristics of 313 consecutive esophageal cancer patients treated with esophagectomy

	No IPC (n=118)		**IPC (n=195)**		**P value ***
Male gender	85	(72%)	141	(72%)	0.958
Age (years) (median, range)	64	(38-78)	65	(39-83)	0.895 †
BMI (kg/m2) (median, range)	25	(16 - 36)	25	(15 - 36)	0.800 †
ASA score					0.746
1	30	(25%)	45	(23%)	
2	69	(58%)	122	(62%)	
3	19	(16%)	27	(14%)	
4	0	(0%)	1	(1%)	
Cardiovascular comorbidity					
History of VTE					0.259
PE	8	(7%)	6	(3%)	
DVT	4	(3%)	4	(2%)	
Cerebrovascular disease	7	(6%)	14	(7%)	0.669
Coronary disease	24	(20%)	51	(26%)	0.259
Hypertension	35	(30%)	74	(38%)	0.150
Use of anticoagulant therapy	9	(8%)	16	(8%)	0.855
Use of antiplatelet drug	24	(20%)	47	(24%)	0.441
Diabetes mellitus	17	(14%)	28	(14%)	0.991
COPD	21	(18%)	37	(19%)	0.795
Chronic kidney disease (serum creat > 110μmol/L)	1	(1%)	9	(5%)	0.096 ‡

BMI body mass index, ASA American Society of Anaesthesiologists, VTE venous thromboembolic event, PE pulmonary embolism, DVT deep venous thrombosis, COPD chronic obstructive pulmonary disease, creat creatinine

* Chi-square test unless otherwise stated, † Mann-Whitney U test, ‡ Fisher's exact test

Anaesthesiologists (ASA) score and comorbidities between patients treated with or without IPC. Regarding histopathology, the majority of the patients were diagnosed with an adenocarcinoma (76%). There were 128 patients (66%) with stage II-IV disease in the IPC-group compared to 89 (75%) in the group without IPC (p=0.069, χ^2 test) (Table 2). In the IPC-group there was a higher proportion of patients in which the tumor differentiation grade could not be assessed (Gx) because of absence of tumor cells in the resected specimen due to either complete response to neoadjuvant therapy or prior endomucosal resection (19% vs. 4%, p=0.006, χ^2 test).

Treatment approach and postoperative course

The number of patients receiving neoadjuvant therapy was higher in the IPC group (77% vs. 38%, p<0.001, χ^2 test) (Figure 1, Table 3). The administration of neoadjuvant chemotherapy was equally distributed among both groups (31% vs 34%, p=0.631, χ^2 test), whereas neoadjuvant chemoradiation was administered more often in the IPC-group (45% vs 3%, p<0.001, χ^2 test). There were no differences with regard to surgical approach (transhiatal/transthoracic), type of surgery (open/minimally invasive), operative time, blood loss and ICU stay between both groups. Patients treated without IPC had a longer hospital stay (median 18 vs 15 days, p=0.014, MWU test). In-hospital mortality was 3% (n=6) in the IPC-group and 4% (n=5) in patients without IPC (p=0.589, χ^2 test).

Venous thromboembolic events

Overall, 12 symptomatic VTE's occurred in 11 patients during the postoperative period of 30 days. All VTE's occurred during the in-hospital stay. The VTE's consisted of a DVT in 2 patients and a pulmonary embolism in 10 patients. In the patient who developed a DVT and a pulmonary embolism, only the first event was used for analysis. Six patients developed a VTE within the first week after surgery and 5 patients between 11 and 28 days after surgery. Median day of VTE was on day 8 after surgery, which did not differ between patients with IPC (day 5) and without IPC (day 9, p=0.918). The rate of VTE in the group of patients who received IPC was 1.5% (3/195) which was significantly lower compared to the 6.8% (8/118) in patients treated without IPC (OR=0.215; 95% CI=0.06-0.83; p=0.025). The incidence of postoperative VTE was reduced by 78%, whereas the absolute risk reduction was 5.3%. To prevent one postoperative VTE, 19 patients needed to be treated with IPC (Numbers needed to treat=18.9). Additional sensitivity analysis was conducted including the patients in whom it is uncertain whether they received IPC (n=19). This did not influence the results.

Prognostic factors

Univariate logistic regression analysis demonstrated that apart from IPC, no other factors showed a significant correlation with the development of postoperative symptomatic VTE's (Table 4). To correct for possible confounding factors, all variables with a univariate p-value below 0.150, which included operative time (p=0.103, MWU test) and length of stay (log, p=0.097, MWU test), were entered in a multivariate logistic regression model (Table 4). The addition of IPC remained as the only independent prognostic factor correlated with a reduced rate of postoperative VTE's (OR=0.225; 95% CI=0.06-0.88; p=0.032). Also, in the additional sensitivity analysis including all 332 patients, IPC significantly reduced the rate of postoperative VTE's in the multivariate analysis (OR=0.226; 95% CI=0.06-0.88; p=0.032).

Table 2 Histopathological characteristics

	No IPC (n=118)	IPC (n=195)	P value*
Tumor Stage			0.069
0-I	29 (25%)	67 (34%)	
II-IV	89 (75%)	128 (66%)	
Tumor type			0.934
AC	89 (75%)	150 (77%)	
SCC	28 (24%)	43 (22%)	
Other	1 (1%)	2 (1%)	
Tumor Differentiation Grade			0.006
Gx	5 (4%)	36 (19%)	
Well	5 (4%)	6 (3%)	
Moderate	48 (41%)	62 (32%)	
Poor	43 (36%)	66 (34%)	
Undifferentiated	2 (2%)	1 (1%)	
Unknown	15 (13%)	24 (12%)	

AC adenocarcinoma, SCC squamous cell carcinoma. Gx grade could not be assessed due to complete response to neoadjuvant therapy or absent tumor cells in the resected specimen due to prior endomucosal resection.
* Chi-squared test

Table 3 Treatment approach and postoperative course

	No IPC (n=118)		IPC (n=195)		P value*
Neoadjuvant therapy					<0.001
None	73	(62%)	45	(23%)	
Chemotherapy	40	(34%)	61	(31%)	
Radiotherapy	1	(1%)	1	(1%)	
Chemoradiation	4	(3%)	88	(45%)	
Surgical approach					0.661
Transhiatal	30	(25%)	54	(28%)	
Transthoracic	88	(75%)	141	(72%)	
Type of surgery					0.698
Open	22	(19%)	33	(17%)	
Minimally invasive	96	(81%)	162	(83%)	
Operative time in minutes‡	383	(304-444)	363	(273-420)	0.050†
Blood loss in mL‡	450	(200-675)	350	(200-550)	0.182†
ICU stay in days‡	1	(1-2)	1	(1-2)	0.201†
Hospital stay in days‡	18	(14-26)	15	(12-25)	0.014†

‡ median (interquartile range)
* Chi-squared unless otherwise stated
† Mann-Whitney U test

8

DISCUSSION

This study demonstrated that the addition of Intermittent Pneumatic Compression (IPC) to conventional Low-Molecular Weight Heparin (LMWH) reduced the incidence of postoperative symptomatic venous thrombotic events (VTE's) by 78% in patients treated with esophagectomy for cancer. In patients receiving IPC, only 1.5% developed a VTE compared to 6.8% in the non-IPC group. This suggests that IPC may prevent the development of VTE during the immobilisation during esophageal cancer surgery as well as during the direct postoperative period in the Intensive Care Unit.

The beneficial effects of IPC have been demonstrated in a variety of surgical procedures. A previous small meta-analysis of 2270 patients demonstrated that IPC was the most effective single VTE prophylactic measure analysed which included aspirin, warfarin and LMWH as independent variables[13]. A more recent meta-analysis

Table 4 Univariate and multivariate analysis of factors affecting the development of postoperative thrombo-embolic complications in patients with esophageal cancer.

	Univariate			**Multivariate**		
	OR	**95% CI**	**P value**	**OR**	**95%CI**	**P value**
Age	0.994	0.93-1.06	0.868			
BMI	1.099	0.95-1.27	0.197			
Cardiac comorbidity						
No	Reference					
Yes	1.193	0.31-4.62	0.799			
Vascular comorbidity						
No	Reference	-				
Yes	0.646	0.14-3.01	0.582			
History of TE						
No	Reference	-	-			
Yes	1.446	0.37-5.61	0.594			
Neoadjuvant therapy						
None	Reference	-	-			
Chemotherapy	0.571	0.14-2.35	0.437			
Chemoradiotherapy	0.415	0.08-2.11	0.288			
Type of resection						
Transhiatal	Reference	-	-			
Transthoracic	1.677	0.36-7.93	0.514			
Operative time	1.005	1.00-1.01	0.103	1.004	1.00-1.01	0.198
Intermittent Pneumatic Compression						
No	Reference	-	-	Reference	-	-
Yes	0.215	0.06-0.83	0.025	0.225	0.06-0.88	0.032
Tumor stage						
0-I	Reference	-	-			
II-IV	0.767	0.22-2.68	0.678			
Length of stay (log)	2.154	0.87-5.44	0.097	2.023	0.75-5.49	0.166
Anastomotic leakage						
No	Reference	-	-			
Yes	1.077	0.28-4.16	0.914			
Pulmonary complications						
No	Reference	-	-			
Yes	0.997	0.29-3.48	0.997			

Analysis was performed using binary logistic regression. All variables with p<0.150 from univariate analyses (Italic) were included in a multivariate analysis using the Enter-method. Bold values indicate statistical significance. TE thrombo-embolism, OR odds ratio, CI confidence interval, BMI body mass index.

that included 70 studies with in total 16 164 hospitalized patients, demonstrated that IPC was more effective than no IPC prophylaxis in reducing deep vein thrombosis and pulmonary embolism with an absolute risk reduction of respectively 9.4% and 1.6%[14]. However, the majority of the included studies reported on the use of IPC in patients undergoing neurological, orthopaedic or general surgery. Only limited studies were available in oncological surgery and none of them reported on esophageal cancer surgery. Thus, to our knowledge this is the first study that analysed the addition of IPC to conventional thromboprophylaxis with LMWH in patients undergoing esophagectomy in patients with cancer.

VTE's after esophagectomy for esophageal cancer remains a clinically important problem. Recent data from the National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons showed that among various oncological procedures esophagectomy has the highest rate of postoperative VTE (7.3%)[2]. Esophagectomy is therefore considered to be a high-risk procedure. This is confirmed by the current study in which a VTE rate of 6.8% was found in patients treated with conventional LMWH alone. Reducing the lengths of immobilisation after esophagectomy with the increasing use of minimally invasive surgery and postoperative enhanced recovery programs has helped to decrease the incidence of VTE's, but they are still considered to be a significant cause of potentially preventable morbidity and mortality among esophageal cancer patients, which is confirmed by a recent study that showed a doubled mortality rate in patients operated for esophageal cancer who developed VTE[15-17]. Literature supports the use of VTE chemoprophylaxis in surgical patients, especially for high-risk procedures such as esophagectomy. The guidelines from the American College of Chest Physicians (ACCP) strongly suggests to use either low-dose unfractioned heparin (LDUH) or low-molecular weight heparin (LMWH) over no prophylaxis for thoracic surgery patients at high risk for VTE[7]. Also, these guidelines suggest to use additional mechanical prophylaxis with elastic stockings and/or IPC. However, the evidence supporting this recommendation was lacking until now.

At the University Medical Center of Utrecht thromboprophylaxis with IPC was added to the protocol in 2010 on the basis of existing literature in other procedures, in order to reduce the high rate of VTE's in esophagectomy patients. Impressively, the rate could be reduced to a rate as low as 1.5% if patients receive additional IPC treatment. As mentioned before, patients undergoing esophagectomy experience a long period of immobilization during surgery and during the immediate postoperative period. This results in a reduced flow velocity in deep veins, which could lead to the formation of blood clots. By mimicking the action of the leg muscle pumps with the compressions of IPC, the flow velocity is increased and venous stasis is reduced[18]. Also, the increased venous volume flow and increased flow velocity results in increased shear stress[19]. Previous animal studies demonstrated that these changes result in endothelial cell responses that contribute to the profibrinolytic, vasodilatory, and antithrombotic effects of IPC[18]. Furthermore, a previous study has also shown that the effect of IPC on endogenous fibrinolytic activity by the increased production of several platelet activation inhibitors may also reduce postoperative VTE [20].

The strengths of this study are that this is the first study reporting on the use of IPC in a large consecutive series of patients treated with esophageal cancer surgery. However, some potential limitations should be addressed. Although a prospective database was used to collect all data, the retrospective design of study confers to potential selection bias. As such, we found several differences between both groups. At first, in the group receiving IPC more patients received neoadjuvant chemoradiation, which was introduced in 2012 at our institution. As a result, more patients were treated with neoadjuvant therapy in the IPC-group compared to the non IPC-group. Nevertheless, the VTE rate was the lowest in the IPC group although neoadjuvant therapy would have made them more prone to VTE. Furthermore, several studies have shown that the administration of neoadjuvant chemotherapy or neoadjuvant chemoradiation only resulted in an increased risk of VTE's preoperatively, but does not affect the development of VTE's after surgery [21, 22]. Secondly, in-hospital stay was prolonged from 15 days in the IPC-group to 18 days in the non IPC-group. This is most probably due to improvements in modern esophageal surgery and postoperative care. We have, however, corrected for in-hospital stay in the multivariate regression model and the use of IPC remained as the only independent prognostic factor correlated with a reduced rate of VTE, thus limiting the chance of potential bias. Lastly, we did not routinely screen for VTE's. Therefore, the VTE's found in this study were only the symptomatic VTE's and the true incidence would likely be higher due to patients with non-symptomatic VTE's.

In conclusion, the addition of IPC to conventional thromboprophylaxis with LMWH reduced the incidence of venous thromboembolic events and reduced the length of in-hospital stay in patients treated with esophageal cancer surgery. This study suggests that mechanical IPC treatment in combination with standard thromboprophylaxis may be a viable and effective prophylaxis against VTE in this high risk population.

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Chapter 9

Hiatal hernia following esophagectomy for cancer.

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ABSTRACT

Background

Hiatal hernia (HH) after esophagectomy is becoming more relevant due to improvements in survival. This study aimed to evaluate and compare the occurrence and clinical course of HH following open and minimally invasive esophagectomy (MIE).

Methods

The prospectively recorded characteristics of patients treated with esophagectomy for cancer at two tertiary referral centers in the United Kingdom and the Netherlands between 2000-2014 were reviewed. All computed tomography reports were reviewed to identify HH.

Results

Of 657 patients, MIE was performed in 432 (66%) and open esophagectomy in 225 (34%) patients. A computed tomography scan was performed in 488 (74%) patients. HH was diagnosed in 45 patients after a median of 20 (0-101) months. The development of HH after MIE was comparable to the open approach (8% vs. 5%, p=0.267). A total of 14 patients presented as a surgical emergency at the time of diagnosis. Of the remaining 31 patients, 17 were symptomatic and 14 were asymptomatic. Elective surgery was performed in 10 symptomatic patients, all others were treated conservatively. During conservative treatment, 2 patients presented as a surgical emergency. Emergency surgery resulted in a prolonged intensive care unit stay compared to elective surgery (3 vs. 0 days, p<0.001). In-hospital mortality was solely seen after emergency surgery (19%).

Conclusion

HH is a significant long-term complication after esophagectomy, occurring in a substantial proportion of the patients. The occurrence of HH after MIE and open esophagectomy is comparable. Emergency surgery is associated with dismal outcomes and should be avoided.

INTRODUCTION

Esophagectomy is the cornerstone of multimodality treatment for esophageal cancer. This includes dissection and removal of the esophagus, followed by restoration of the alimentary tract with a gastric tube in the majority of cases[1, 2]. During this procedure, the normal anatomy around the esophageal hiatus of the diaphragm is disrupted, which could lead to an increased risk of developing a postoperative hiatal hernia (HH). A recent systematic review reported a mean HH incidence of 2.6%, occurring up to 32 months after surgery[3]. This is likely to be an underestimate of the true incidence due to the limited long-term survival in the included studies and because some studies only reported rates of HH requiring surgical repair[3]. With improvements in overall survival due to the routine use of neoadjuvant treatment and modern-day esophageal cancer surgery[4], the development of HH after esophagectomy is becoming more relevant.

Minimally invasive esophagectomy (MIE) has been performed more frequently in recent years due to promising short-term outcomes such as decreased postoperative morbidity, shorter hospital stays and faster recovery[2, 5, 6]. These potential benefits could be offset by short and long-term complications specific to the minimally invasive approach. There is surgical concern that HH presenting as a surgical emergency, with potentially catastrophic consequences, is increasingly being seen in patients who are long-term survivors after MIE[7-9]. The aims of the current study were to document the occurrence and clinical course of HH following open and minimally invasive esophagectomy.

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PATIENTS AND METHODS

Study population

Consecutive patients treated with transhiatal or transthoracic esophagectomy followed by gastric tube reconstruction at two designated cancer centers from the United Kingdom (UK) and the Netherlands were reviewed (October 2000 - December 2014). All patients were diagnosed with a clinically resectable tumor (cT1a-T4aN0-3M0) according to the American Join Committee on Cancer (AJCC) Tumor Node Metastases (TNM) staging system[10]. A small group of patients who underwent a hybrid procedure procedure (n=37), or who died in the hospital during the postoperative course were excluded. Neoadjuvant therapy was given to eligible patients with locally advanced tumors (≥T2 or N+) and consisted of perioperative chemotherapy or neoadjuvant chemoradiation as previously described[4, 11]. In the UK, most patients received perioperative chemotherapy. In the Netherlands, most patients received perioperative chemotherapy before 2012. Hereafter, due to the results of the CROSS-trial most patients received neoadjuvant chemoradiotherapy. Institutional Review Board approval for both centers was obtained and informed consent requirement was waived for this study.

Surgical procedure

In all patients, an esophagectomy with gastric tube reconstruction was performed, including Ivor Lewis, McKeown, and transhiatal esophagectomy. All types of procedures were performed minimally invasive and open based on institutional, surgeon and patient preference. The McKeown and transhiatal approach were predominantly performed at University Medical Center Utrecht (UMC Utrecht), Netherlands, whereas the Ivor Lewis procedure was predominantly performed at University Hospital Southampton (UHS), UK. The surgical procedures were performed as previously described[6, 12]. In the UMC Utrecht, a robot-assisted minimally invasive transthoracic approach is used in case of a MIE. This includes a robot-assisted thoracoscopic phase in the left lateral decubitus position, with 3 ports placed for the robot and 2 ports for the assistant. For both the abdominal phase of the transthoracic esophagectomy as for the transhiatal esophagectomy, the patient is placed in a supine position and 5 ports are used for dissection and lymphadenectomy. After that, the left para-umbilical trocars port is widened to a 5-7cm transverse transabdominal incision for removal of the specimen. In the UHS the Ivor Lewis procedure starts with abdominal laparoscopy in supine position via 5 ports for gastric mobilization and lymphadenectomy. After that, a thoracoscopic esophageal mobilization and mediastinal lymphadenectomy using 3 ports in prone position is performed. For removal of the resected specimen, the lower most thoracic port is enlarged to 3–6cm. In both centers, a 4-5cm gastric tube was constructed and positioned prevertebrally, in the esophageal bed, and cruroplasty and fixation of the gastric tube were not performed in any patient. The intraoperative techniques were comparable for open esophagectomy and MIE.

Evaluation of hiatal hernia

Postoperative follow-up of all surviving patients took place every 3 months in the first year, every 6 months in the second and third year and every 12 months thereafter until discharge of follow-up after 5 years. According to national guidelines, patients did not undergo routine imaging during follow-up, but only underwent radiological imaging or endoscopy if they were symptomatic suggestive of tumor recurrence, or long-term complications[13-15]. To identify HH, all computed tomography (CT) reports of patients who underwent a scan ≥2 months after surgery were reviewed. HH was defined as herniation of abdominal organs other than the gastric tube into the thorax. The electronic patient records were reviewed to evaluate the clinical course associated with HH including clinical presentation, treatment, and postoperative course after surgical repair. Patients were considered symptomatic if imaging was performed for symptoms that may have been attributable to HH (e.g. pain, dysphagia, vomiting or dyspnea). Patients who underwent imaging for other indications were defined as "asymptomatic". The percentages of HH was calculated in the group of patients who had a follow up CT scan and in all patients.

Hiatal hernia treatment

During the study period, there was no standardized treatment protocol for HH following esophagectomy. In general, asymptomatic patients were treated with a watchful waiting policy (conservative management). The treatment of symptomatic patients was based on individual assessment of symptoms, patient fitness, risk factors and prognosis. Surgical repair of HH was performed through an open or minimally invasive abdominal approach. During the procedure, the content of the HH was dissected completely from the mediastinal structures and returned to the abdomen, the hiatal defect was repaired by approximation of the left and right crus, and a mesh was performed according to the surgeon's preference. Lastly, the gastric conduit was attached to the crus.

Statistical analysis

First a comparison was made between the UHS and UMC Utrecht to determine the equality of both databases regarding patient demographics. Data were evaluated by means of the Mann-Whitney U (MWU) test for continuous variables and the Pearson's Chi-squared (χ^2 test) – or Fisher's exact test in case of small cell count – for categorical variables. To determine risk factors for HH, factors with a p-value <0.250 on univariable analysis were entered in a multivariable logistic regression model. To compare the incidence of HH after MIE and open esophagectomy, propensity score matching (PSM) was used to build comparable groups and to deal with possible confounding factors. The optimal matching technique was used to generated matched sets of cases in which each set contain one open esophagectomy case and one MIE case[16]. Covariate balance of the matched cohort was assessed using the mean standardized differences, with differences less than 10% taken to indicate good balance[17]. Data were considered significant if p<0.05. Data were analyzed using the IBM SPSS Statistics (version 21; IBM Corporation, Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages) for PSM.

RESULTS

Patients

A total of 657 consecutive patients underwent transhiatal or transthoracic esophagectomy for esophageal cancer (Table 1). MIE was performed in 432 (66%) patients; open esophagectomy in 225 (34%) patients. Patients treated at UHS had a higher American Society of Anesthesiologists (ASA) score (ASA 3: 24% vs. 17%, p<0.001) and underwent open surgery more often (46% vs 25%, p<0.001). A transhiatal approach was only performed in the UMC Utrecht. All other parameters were comparable.

Hiatal hernia

The median follow-up of the entire cohort was 31 months (range 6-107). In total, 488 (74%) underwent a CT-scan during follow-up. The last CT-scan of each patient was performed at a median of 18 months (range 2-149). A total of 45 patients were diagnosed with a HH; 7% (45/657) of the total study population and 9% (45/488) of the patients who underwent a CT-scan. At diagnosis, 31/45 (69%) patients experienced symptoms; 5% (31/657) of the total study population. Of the remaining 14/45 (31%) asymptomatic patients, HH was an incidental finding. The HH was located in the left chest in 41 (91%) patients and involved the colon in 37 (82%) patients, the small intestines in 19 (42%) patients (Figure 1), the pancreas in 6 (13%) patients, the liver in 3 (7%) patients and the spleen in 1 (2%) patient. The median time of HH diagnosis was 20 months (range 0-101) after esophagectomy. Figure 2 demonstrates the time from surgery to HH diagnosis of all patients for patients presenting electively (31; 69%) coand patients presenting as a surgical emergency (14; 31%) Of note, 203 (31%) patients died before the median time of HH diagnosis (20 months), and in 33 (5%) patients follow-up did not yet reach the median time of HH diagnosis of 20 months.

Of the 31 patients who presented electively, 17 (55%) were symptomatic, with abdominal or thoracic pain as the most common presenting symptom, and 14 (45%)

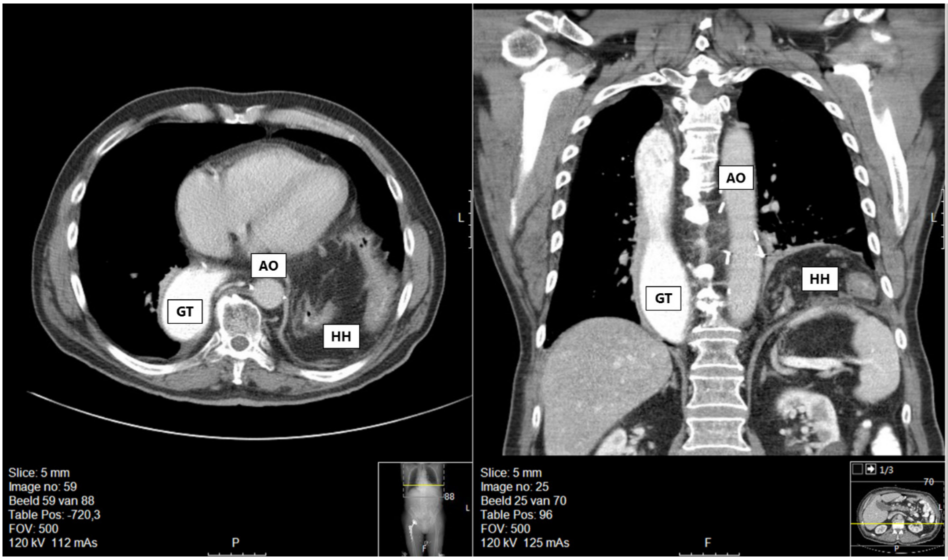

Figure 1 HH of the small intestines after esophagectomy. GT; Gastric Tube. AO; Aorta. HH; Hiatal hernia.

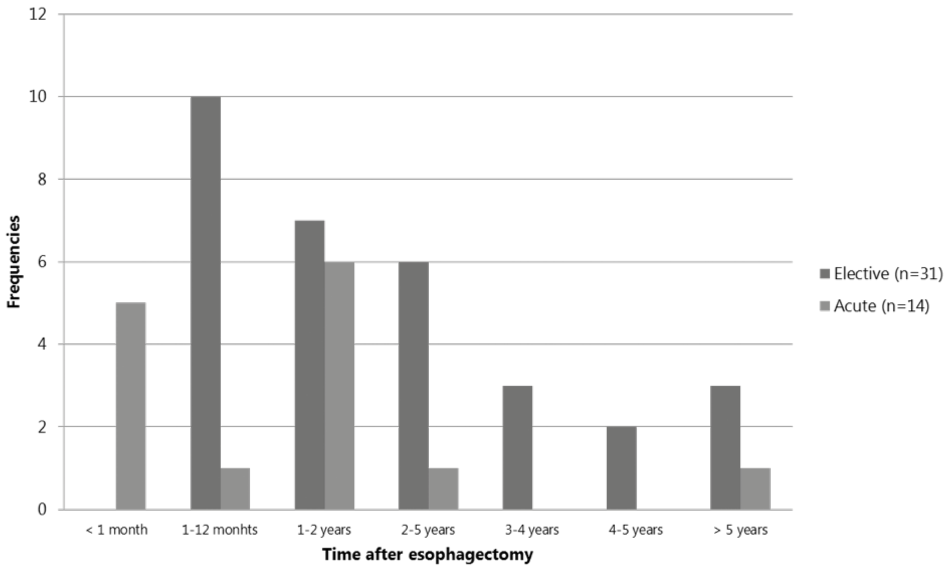

Figure 2 Time to diagnosis of HH after esophagectomy according to presentation at diagnosis.

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were asymptomatic (Figure 3). All 14 patients who presented as a surgical emergency experienced acute symptoms. Only 4 of these patients had symptoms in the weeks before presentation that could be attributable to HH, whereas the other 10 patients experienced a sudden onset of symptoms.

Treatment

All 14 patients who presented as an emergency underwent immediate surgery (Figure 3). In the remaining 31 patients, elective surgery was performed in 10 symptomatic patients. All other patients (7 symptomatic; 14 asymptomatic) were treated conservatively. After a median follow-up of 14 (0-66) months, conservative management was successful in 19 patients, whereas 2 patients (1 symptomatic; 1 asymptomatic) needed emergency surgery. As a result, in total 16 patients required emergency surgery. During emergency surgical repair, 12 patients underwent a laparotomy and 4 patients underwent laparoscopy. One conversion occurred. For elective repair, 4 patients underwent laparotomy and 6 patients underwent laparoscopy. A mesh was used in 5 patients.

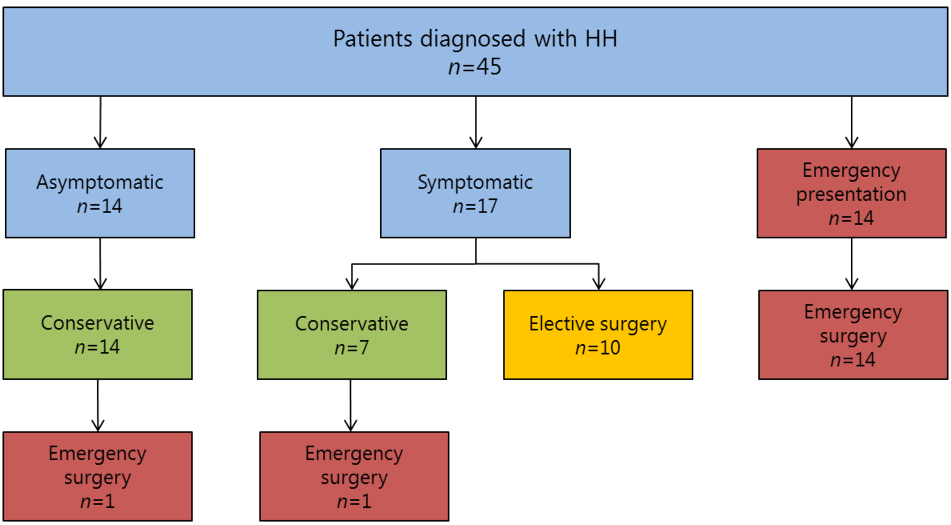

Figure 3 Flowchart of treatment decisions at the time of HH diagnosis.

Clinical course

Postoperative complications occurred in 8/16 (50%) patients after emergency and in 1/10 (10%) patient after elective surgery (p=0.087). Complications included pneumonia (n=5), atrial fibrillation (n=3), bowel ischaemia (n=1), pleural effusion (n=1) and anaphylactic reaction to anesthetics (n=1). In-hospital mortality was only seen after emergency surgery (n=3, 19%); two patients died due to pneumonia and one patient died due to an anaphylactic reaction of anesthetics. A total of 15 patients who underwent emergency surgery were admitted to the Intensive Care Unit (ICU) for a median of 3 (0-18) days, compared to none after elective surgery (p<0.001). Median hospital stay was 10 (4-121) days after emergency surgery compared to 4 (1-17) days after elective surgery (p=0.051). After a median follow-up of 9 (range 0 – 65) months, recurrent HH was found in 4 (15%) patients after surgical repair, regardless of mesh (1 mesh vs. 3 no mesh, p=1.000) and surgical procedure (3 laparotomy vs. 1 laparoscopy, p=0.604). HH recurrence was treated by redo surgery in 2 (50%) patients; the other 2 were treated conservatively. Of all patients with HH, 3 (7%) died during hospital admission of HH repair, 20 (44%) died due to non-hernia related causes, and 22 were alive after a median follow-up of 14 (0-66) months.

Risk factors

A comparison was made between patients who developed HH and patients who did not develop HH after esophagectomy (Table 1). The univariable analysis demonstrated no differences. The multivariable analysis included all patient and tumor characteristics with p<0.250 (Table 2), and demonstrated that a low BMI (<25 kg/m2) (OR 2.0, 95% CI [1.1 – 3.7] p=0.026) was associated with HH.

Open vs. Minimally Invasive Esophagectomy

In the original cohort, differences in baseline were found between the open esophagectomy and MIE group (Table 3). After PSM however, the 2 groups were well-balanced with 225 patients in each group. The development of HH after MIE was comparable to the open approach (7% vs. 5%, p=0.559) with similar follow-up in both groups (28 vs. 26 months, p=0.405).

Table 1 Comparison of patients with and without hiatal hernia after esophagectomy.

	Hiatal hernia (n=45)		No hiatal hernia (n=612)		
	n	**(%)**	**n**	**(%)**	**p-value**
Gender					0.196
Male	38	(8)	465	(92)	
Female	7	(5)	147	(95)	
Age (years) a	62.8	[8.1]	65.0	[9.3]	0.118
BMI during esophagectomy (kg/m2) a	24.7	[3.5]	26.1	[4.0]	0.029
Smoking history	29	(64)	322	(53)	0.158
ASA					0.888
I	9	(7)	112	(93)	
II	29	(7)	376	(93)	
III	7	(5)	123	(95)	
IV	0	(0)	1	(100)	
Neoadjuvant therapy					0.657
None	12	(5)	214	(95)	
Chemotherapy	24	(8)	276	(92)	
Radiotherapy	0	(0)	2	(100)	
Chemoradiotherapy	9	(7)	120	(93)	
pT-stage					0.943
T0 / CIS	4	(5)	75	(95)	
T1	9	(7)	112	(93)	
T2	8	(8)	92	(92)	
T3	23	(7)	313	(93)	
T4	1	(5)	20	(95)	
Tumor location					0.243
Upper 1/3	0	(0)	4	(100)	
Middle 1/3	2	(3)	67	(97)	
Lower 1/3	21	(7)	302	(93)	
GEJ	22	(9)	225	(91)	
Procedure type					0.265
Open					
Ivor Lewis	5	(4)	122	(96)	
McKeown	2	(4)	52	(96)	
Transhiatal	5	(11)	39	(89)	
MIE					
Ivor Lewis	13	(10)	118	(90)	
McKeown	17	(7)	215	(93)	
Transhiatal	3	(4)	66	(96)	

Table 2 Univariable and multivariable logistic regression of risk factors associated with the occurrence of HH after esophagectomy.

All patients (n=657)						
	Univariable			**Multivariable**		
	OR	**95% CI**	**p**	**OR**	**95%CI**	**p**
Male gender	1.7	[0.8 – 3.9]	0.201	1.8	[0.8 – 4.1]	0.191
BMI <25 kg/m2	1.9	[1.0 – 3.5]	0.037	2.0	[1.1 – 3.7]	0.026
MIE	1.5	[0.7 – 2.9]	0.269	1.4	[0.7 – 2.9]	0.317
Transhiatal	1.0	[0.5 – 2.3]	0.915	-	-	
Age >65	0.6	[0.4 – 1.2]	0.170	0.7	[0.4 – 1.3]	0.234
Smoking history	1.6	[0.8 – 3.0]	0.161	1.4	[0.7 – 2.8]	0.286
ASA 3-4	0.7	[0.3 – 1.7]	0.447	-	-	
CRTx vs. CTx	0.9	[0.4 – 1.9]	0.729	-		
pT-stage 3-4	1.0	[0.5 – 1.8]	0.889	-	-	
GEJ tumor	1.6	[0.9 – 3.0]	0.108	1.7	[0.9 – 3.1]	0.106

DISCUSSION

Major findings

In this large cohort of consecutive patients treated with esophagectomy for cancer, the incidence of postoperative hiatal hernia (HH) was 7-10%. The incidence of HH after MIE was comparable to open surgery. Hiatal herniation presented acutely in 32% of patients, who were at high risk of perioperative death. A conservative management strategy appears to be safe in asymptomatic patients with HH.

Occurrence

HH following esophagectomy is a significant long-term complication, which occurs in a substantial group of patients. In this study, the incidence of 7% from the total study population is probably underestimated, as 26% of the patients did not undergo a CT-scan. On the other hand, the incidence of 10% calculated from patients who underwent a CT-scan probably overestimates the true incidence, as the incidence of HH in patients who did not undergo a CT-scan is probably lower. Thus, the true incidence of HH is most likely between 7-10%. These numbers are comparable to

Table 3 Baseline characteristics and the occurrence of HH of the original and PSM cohort

	Original Cohort (n=657)				
	Open (n=225)		MIE (n=432)		
	n	(%)	n	(%)	p-value
Male gender	181	(80)	322	(75)	0.090
Age (years) (mean, SD)	65.2	±9.4	64.7	±9.2	0.546
BMI (kg/m2) (mean, SD)	26.0	±3.8	26.0	±4.1	0.938
Smoking history					0.013
No	98	(44)	181	(42)	
Yes	111	(49)	240	(56)	
Unknown	16	(7)	11	(3)	
ASA					0.221
I	46	(20)	75	(17)	
II	129	(57)	276	(64)	
III	49	(22)	81	(19)	
IV	1	(0)	0	(0)	
Neoadjuvant therapy					0.316
None	77	(34)	149	(34)	
Chemotherapy	111	(49)	189	(44)	
Radiotherapy	1	(0)	1	(0)	
Chemoradiotherapy	36	(16)	93	(22)	
Surgical approach					<0.001
Ivor Lewis	127	(56)	131	(30)	
McKeown	54	(24)	232	(54)	
Transhiatal	44	(20)	69	(16)	
Histology					0.018
CIS	0	(0)	7	(2)	
Adenocarcinoma	192	(85)	334	(77)	
Squamous cell carcinoma	33	(15)	91	(21)	
Tumor location					0.313
Upper 1/3	0	(0)	4	(1)	
Middle 1/3	22	(10)	54	(13)	
Lower 1/3	113	(50)	217	(50)	
Cardia	90	(40)	157	(36)	
pTNM-stage					0.030
0	13	(6)	55	(13)	
I	58	(26)	96	(22)	
II	56	(25)	119	(28)	
III	98	(44)	160	(37)	
IV	0	(0)	2	(0)	
Hiatal Hernia	12	(5)	33	(8)	0.267

PSM Cohort (n=450)				
Open (n=225)		**MIE (n=225)**		
n	**(%)**	**n**	**(%)**	**p-value**
181	(80)	174	(77)	0.488
65.2	±9.4	65.8	±9.4	0.498
26.0	±3.8	26.1	±3.6	0.754
				0.123
98	(44)	95	(42)	
111	(49)	123	(55)	
16	(7)	7	(3)	
				0.445
46	(20)	36	(16)	
129	(57)	140	(62)	
49	(22)	49	(22)	
1	(0)	0	(0)	
				0.798
77	(34)	77	(34)	
111	(49)	111	(49)	
1	(0)	0	(0)	
36	(16)	37	(16)	
				0.694
127	(56)	123	(54)	
54	(24)	57	(25)	
44	(20)	45	(20)	
				1.000
0	(0)	0	(0)	
192	(85)	192	(85)	
33	(15)	33	(15)	
				0.640
0	(0)	1	(0.4)	
22	(10)	17	(8)	
113	(50)	116	(52)	
90	(40)	91	(40)	
				0.323
13	(6)	19	(8)	
58	(26)	54	(24)	
56	(25)	68	(30)	
98	(44)	83	(37)	
0	(0)	1	(0.4)	
12	(5)	16	(7)	0.559

9

a recent meta-analysis and a recent UK study[16, 17], which reported an incidence of 5% and 6% respectively. HH following esophagectomy will become an increasing problem as cancer survival improves. All surgeons discuss mortality and short-term complications at the time of primary resection with their patients, but HH was not specifically considered in a recently defined core disclosure information set for patients undergoing esophagectomy[18]. Patients clearly prioritized other outcomes such as eating, drinking and overall quality of life, which can be significantly impacted by the development of HH and subsequent surgery. This makes the disclosure of the potential for HH after esophagectomy and the identification of risk factors for HH important.

In this study, lower BMI was associated with a higher risk of developing a HH following esophagectomy. A lower BMI has been reported as a risk factor for HH post-esophagectomy before by Ganeshan et al[9]. An explanation could be that a higher BMI results in a reduced mobility of intra-abdominal structures.

The influence of MIE on the occurrence of HH is currently an important topic of debate. In a recent meta-analysis of 6058 patients a higher incidence of a symptomatic HH was found after MIE (4.5%) compared to open esophagectomy (1.0%)[16]. A frequently reported explanation is the reduced formation of peritoneal adhesions after MIE, although there is no evidence to prove this theory. Unfortunately, the included studies in this meta-analysis were heterogeneous. In the present study the overall incidence of HH between the open and minimally invasive group was similar before and after PSM. Due to improvements in overall survival, HH will become a more common problem facing esophageal surgeons and strategies to mitigate HH will need to be considered. A possible prevention method could be closure of the crurae during initial esophagectomy, which is advocated by some surgeons[7]. Crural closure can be performed from the abdomen during a 3-phase McKeown or transhiatal esophagectomy, and from the thorax during a 2-phase Ivor Lewis esophagectomy. However, there is no solid evidence supporting this technique and large studies will be required to validate this.

Diagnosis

In this study the acute presentation of HH was associated with high mortality (19%), which is in keeping with recent data[17]. Surviving patients were at risk of significant complications and long ICU stay. Unfortunately, 14 out of the 16 patients that underwent emergency surgery were not diagnosed with HH before and presented with acute symptoms at diagnosis. Whether HH was already present in these patients remains unclear: only a minority of the patients had mild nonspecific symptoms, which suddenly became worse, but the majority had an acute onset of symptoms. As many patients have non-specific symptoms after esophagectomy, differentiation between HH and non-HH symptoms is difficult. Another option for HH detection could be routine screening. Based on the results in this study, one might perform routine screening at 12-18 months.

Treatment

The current study evaluated treatment decisions made in patients with HH. Although there was no standardized treatment protocol, all asymptomatic patients were initially treated conservatively at the time of HH diagnosis. This is in line with the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines of the treatment of asymptomatic HH in the general population[21]. In contrast, some surgeons advocate surgical repair in all patients, including asymptomatic patients, to prevent emergency surgery after an acute presentation[7, 19]. However, the risk for acute presentation should be balanced against the risks of surgery and patient prognosis. In this study only 1 (7%) asymptomatic patient who was treated conservatively eventually needed emergency surgery. In addition, some of the patients died from non-hernia related causes. Therefore, in asymptomatic patients conservative management appears to be safe. For patients with symptomatic HH in the general population, the SAGES guidelines recommend surgical repair due the high risk of emergency presentation compared to asymptomatic patients[20, 21]. Since evidence concerning the management of symptomatic HHs after esophagectomy is lacking, it remains unclear if the SAGES guidelines should also be followed for this population. In the present study, conservative treatment was successful in 90% of symptomatic patients. Whether to perform surgery in these patients should therefore depend on the severity of symptoms, patient fitness and prognosis taking into account the outcomes of surgery for HH in the emergency setting.

Limitations

There are some limitations of this study that should be addressed. First, there were some baseline differences between the 2 participating centers. Second, this study did not evaluate the preoperative occurrence of HH, which could influence the risk of developing postoperative HH. Third, due to the retrospective character of this study, lack of routine imaging, and short follow-up of some patients, the exact incidence of HH might be underreported. Nevertheless, 73% of all patients could be evaluated and 7-9% developed a HH, which demonstrates the significance of this long-term complication. Fourth, although the reconstruction route during esophagectomy performed in this study is a commonly performed approach, the results may not be generalizable to other procedures. Last, there is selection bias in the chosen treatment for HH. Currently, there is no standard treatment for HH after esophagectomy and therefore the chosen treatment is based on the surgeon's individual preferences.

CONCLUSION

In conclusion, as HH after esophagectomy is expected to occur more frequently in the future due to prolonged survival, more attention is warranted for this significant long-term complication. HH following MIE and open esophagectomy is comparable, but a low BMI was associated with a higher risk for HH. Since a substantial number of patients with HH require emergency surgery, which is associated with poor outcomes, focus should lie on prevention. After elective presentation, conservative management appears to be safe for asymptomatic patients, whereas individual risk assessment should determine the need for surgical therapy in symptomatic patients.

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Chapter 10

Influence of the location of positive lymph nodes on survival in patients with gastroesophageal junction tumors.

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Submitted

ABSTRACT

Background

The aim of this study is to analyze the importance of the location of metastatic lymph nodes in terms of survival in patients with adenocarcinoma of the gastroesophageal junction (GEJ).

Methods

From a prospective database (2003–2014) 199 consecutive patients with a histopathological proven adenocarcinoma of the GEJ treated with transthoracic esophagectomy were included. Univariable and multivariable analysis was used to determine prognostic factors for overall survival.

Results

Neoadjuvant chemotherapy and chemoradiation was administered in 82 (41.2%) and 67 patients (33.7%), respectively. Nodal metastases were found in 116 patients (58%). Upper mediastinal nodal involvement (UM+) was seen in 27 patients (14.1%), whereas 80 patients (41.9%) had pN+ disease without metastatic UM nodes (UM-). Patients with UM+ had a higher pN-stage compared to patients with UM- ($P<0.001$). 34.9% of patients without nodal metastasis developed recurrent disease, compared to 65.2% of pN+/UM- patients and 83.3% of UM+ patients ($p<0.001$). Patients with pN0 had a 5-year survival of 63%, patients with pN+ and UM- 29%, and patients with UM+ 14% ($p=0.031$). pN+ disease was seen in 79.2% in patients without neoadjuvant therapy and in 53.8% and 42.9% of patients after chemotherapy and chemoradiation, respectively. On multivariable analysis, pT3/T4a tumor and UM+ were independent prognostic factors for overall survival.

Conclusion

Location of metastatic lymph nodes is important for the prognosis of patients with an adenocarcinoma of the GEJ. Patients with positive upper mediastinal nodes are likely to develop recurrent disease and consequently have a poor overall survival.

INTRODUCTION

Adenocarcinoma of the gastroesophageal junction (GEJ) is an important clinical entity due to the vast increase in the past few decades[1]. The long-term survival after resection remains poor due to the often advanced stage at the time of diagnosis. Current treatment of this high burden disease consists of neoadjuvant chemo(radio) therapy followed by esophagectomy[2, 3]. It is known that adenocarcinoma of the GEJ can spread to lymph nodes in the mediastinum, upper abdomen and even retroperitoneal regions[4, 5]. Many studies have shown that the presence of metastatic lymph nodes is a strong prognostic predictor of overall survival[6-8]. The 5-year survival rate significantly decreases from 56% in patients without nodes involved to 17% in patients with >7 nodes involved[8]. Therefore, a thorough lymphadenectomy is considered to be essential in addition to surgical resection of the tumor. In the latest TNM staging system by the American Joint Committee on Cancer (AJCC) the location of the metastatic lymph nodes is not considered as a staging determinator. The aim of this study was to analyze the importance of the location of metastatic lymph nodes in terms of survival in patients with an adenocarcinoma of the gastroesophageal junction. A second aim was to evaluate the effect of neoadjuvant therapy on the number and distribution of metastatic lymph nodes.

PATIENTS AND METHODS

A prospective database (July 2003 – December 2014) was used to include consecutive patients with a histopathological proven adenocarcinoma of the GEJ (Siewert type I – II) treated with transthoracic esophagectomy at the University Medical Center Utrecht. In all patients, surgery with curative intent was performed (cT1-4a, N0-3, M0). Preoperative staging included upper endoscopy combined with endoscopic ultrasound (EUS), thoracoabdominal Computerized Tomography (CT) and ultrasound of the neck was performed in all patients. Those who presented with a suspected lesion on CT or ultrasound of the neck without the possibility for histopathological confirmation had a diagnostic Positron Emission Tomography (PET-CT) scan. The 7th edition of the TNM staging system was used for tumor staging. Patients in whom definitive histopathology revealed M1 disease and patients who died in hospital following surgery were excluded from the survival analysis. Institutional Review Board approval was obtained and there was no need for informed consent.

Treatment strategy

Patients were treated with neoadjuvant therapy if they had locally advanced tumors (≥cT2) or with cN+ disease according to national guidelines. Before June 1 2012 all patients received perioperative chemotherapy[3]. After that date, guidelines were changed and patients with a Siewert type I tumor were treated with neoadjuvant chemoradiation[2]. Patients with a type II tumor received either perioperative chemotherapy or neoadjuvant chemoradiation, depending on diagnostic findings and evaluation of these findings in a multidisciplinary expert meeting. Some patients did not have neoadjuvant therapy because of the following reasons: neoadjuvant therapy was not yet incorporated in the treatment protocol, weight loss >10%, WHO performance status ≥2 or patient request. All patients underwent a transthoracic approach with extended en-bloc 2-field lymphadenectomy. A paratracheal lymphadenectomy was routinely performed. A 4-5 cm gastric tube was constructed and positioned prevertebrally with cervical anastomosis in all patients (McKeown)[9]. Both open and minimally invasive procedures were performed with comparable surgical techniques.

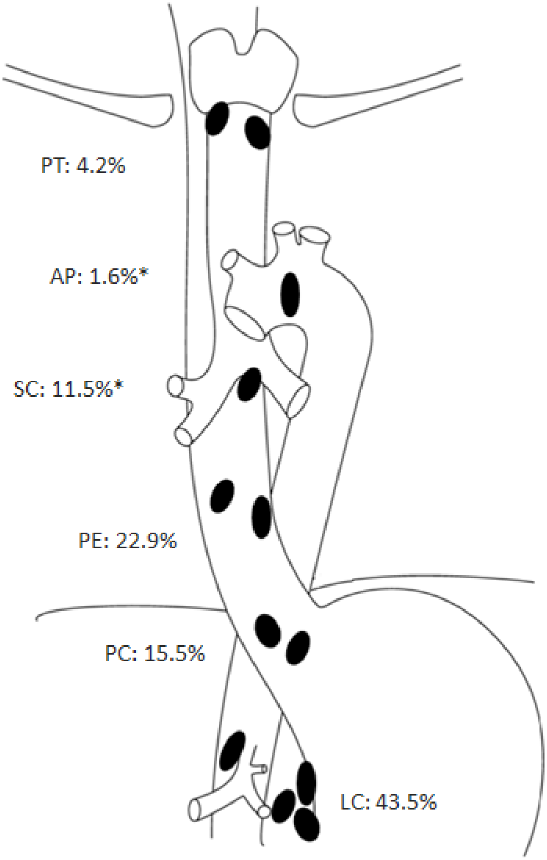
Nodal status

To determine the presence of metastatic lymph nodes, the resected specimens were assessed by a pathologist specialized in gastrointestinal pathology. Nodal stations were defined in accordance with the American Joint Commission on Cancer[10]. The following stations were evaluated: paratracheal (stations 2R and 2L), aortapulmonary window (station 5), subcarinal (station 7), para-esophageal (stations 8M and 8L), paracardial (stations 15 and 16) and lesser curvature (stations 17, 18 and 20). The lesser curvature nodes included the nodes in the hepatoduodenal ligament (not specified in AJCC), along the common hepatic (station 18) and left gastric artery (station 17) and truncal nodes (station 20). During surgery, the paratracheal, subcarinal, para-esophageal and left gastric artery stations were marked for histopathological analysis. We have chosen to not identify the lesser curvature stations separately because en-bloc removal of these nodes with the resection specimen prohibits a reliable evaluation of all stations separately. In a very small subgroup of patients the exact location of some of the positive lymph nodes was unknown, these were reported as missing.

Follow up

All patients were followed regularly for 5 years at the outpatient clinic. Patients were seen every 3 months in the first year, every 6 months in the second year and every 12 months thereafter. Follow-up consisted of medical history and physical examination.

Figure 1 Distribution of metastatic lymph nodes of the study population.



PT = paratracheal, AP = aortapulmonary window, SC = subcarinal, PE = paraesophageal, PC = paracardial, LC = lesser curvature.

Radiological imaging was performed on indication in symptomatic patients suggestive of tumor recurrence or long-term complications. Patient survival was calculated between date of surgery and date of death or last follow up. Disease-free survival was calculated between date of surgery and date of recurrent disease.

Statistical analysis

Analyses were performed with IBM SPSS statistics (version 21; IBM Corporation, Armonk, NY). Nonparametric, continuous data were presented as median with interquartile range (IQR). To evaluate differences between N+ patients with and without UM nodes, the Chi-square test [or Fisher's exact test in case of small cell count] was used. The Kaplan-Meier method was used to estimate disease-free and overall survival. Differences between groups were assessed by means of the log-rank test. Univariable Cox regression was performed to identify variables associated with overall survival. All factors with a p-value <0.100 were entered in a multivariable Cox regression analysis. A p-value < 0.05 was considered significant.

RESULTS

A cohort of 199 consecutive patients underwent transthoracic esophagectomy for adenocarcinoma of the GEJ during the study period. Baseline characteristics are presented in Table 1. Mean age was 62.4 years (standard deviation [SD] ±8.9) and most of them were males (n=168, 84.4%). The majority had an ASA-score of 2 (n=127, 63.8%). Perioperative chemotherapy was administered in 82 patients (41.2%), whereas neoadjuvant chemoradiation was given to 67 patients (33.7%). A minimally invasive transthoracic esophagectomy was performed in 169 patients (84.9%). Location of the tumor was Siewert type I in 65 patients (32.7%) and type II in 114 (57.3%). In 20 patients the histopathological tumor location could not be determined due to complete response to neoadjuvant therapy. Most of the patients had a pT3 tumor (n=111, 55.8%). A radical resection was achieved in 179 patients (89.9%). Ten patients (5%) died due to postoperative complications (in-hospital mortality) and in 2 patients (1.0%) M1 disease was discovered intraoperatively. These patients were excluded from the survival analysis.

Nodal status

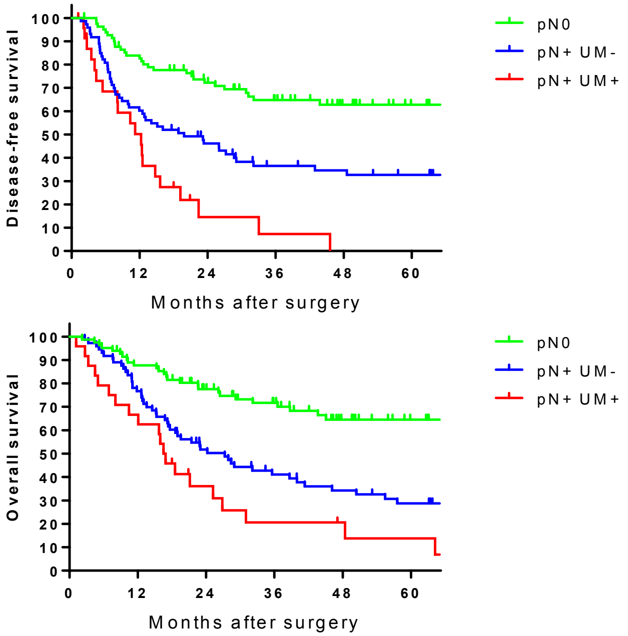
A median number of 22 lymph nodes (IQR 16-29) were harvested during surgery with a median of 1 positive lymph node per patient (IGR 0 – 4, Table 1). A total of 116 patients (58.0%) had lymph node metastases on postoperative histopathological analysis which involved 1-2 lymph nodes in 54 patients (N1, 27.0%), 3-6 lymph nodes in 43 patients (N2, 21.0%) and >7 in 20 patients (N3, 10%). Most patients had positive lymph nodes located at the lesser curvature (n=84, 43.5%) followed by para-esophageal (n=44,

Table 1 Baseline and histopathological characteristics of the study population.

	All patients n=199	
Age (mean ±SD)	62.4y	±8.9
Male gender	169	84.4%
BMI (mean ±SD)	26.1	±4.2
ASA – classification		
1	50	25.1%
2	127	63.8%
3	22	11.1%
Neoadjuvant therapy		
None	48	24.1%
Chemotherapy	82	41.2%
Chemoradiation	67	33.7%
Radiotherapy	2	1.0%
Type of surgery		
Open	30	15.1%
Minimally invasive	169	84.9%
Siewert classification		
Type 1	65	32.7%
Type 2	114	57.3%
No malignancy	20	10.1%
pT-stage		
T0	20	10.1%
Tis	1	0.5%
T1	24	12.1%
T2	37	18.6%
T3	111	55.8%
T4a	6	3.0%
pN-stage		
N0	83	41.7%
N1	54	27.1%
N2	42	21.1%
N3	20	10.1%
pM-stage		
M0	198	99.0%
M1	2	1.0%
Total harvested lymph nodes (median, IQR)	22.0	16 – 29
Total positive lymph nodes (median, IQR)	1.0	0 – 4
Completeness of resection		
R0	179	89.9%
R1	20	10.1%

BMI = body mass index, ASA = American Society of Anaesthesiology, IQR = interquartile range

Figure 2 Survival curves by the Kaplan Meijer method in all patients according to the location of metastatic lymph nodes. A: disease-free survival B: overall survival.



UM = upper mediastinum

22.9%), paracardial (n=15, 15.5%), subcarinal (n=22, 11.5%), paratracheal (n=8, 4.3%), and aortapulmonary window (n=3, 1.6%). Upper mediastinal nodal involvement (UM+), which included the subcarinal, aortapulmonary window and paratracheal stations, was seen in 27 patients (14.1%), whereas 80 patients (41.9%) had pN+ disease without UM lymph node involvement (UM-).

A subgroup analysis was performed in patients with pN+ disease with and without UM nodal involvement. No differences were found between both groups regarding the location of the tumor (Siewert classification) and pT-stage (Table 2). Patients with UM+ had a higher pN-stage (p=0.001) with significantly more positive lymph nodes per patient (5 vs. 2, p=0.001) compared to patients with UM-. A radical resection could be achieved in 74.1% in patients with UM+ compared to 87.5% in patients with UM- (p=0.099).

Neoadjuvant therapy

Differences were found in the distribution of metastatic lymph nodes between patients without neoadjuvant therapy and those treated with chemotherapy or chemoradiation (Table 3). In patients without neoadjuvant therapy, no nodal involvement was seen in 20.8% compared to 46.2% in patients treated with chemotherapy and 57.1% in patients treated with chemoradiation. UM+ was found in 18.4% of the patients without neoadjuvant therapy compared to 11.5% in patients with chemotherapy and 14.3% in patients with chemoradiation (p=0.003).

Table 2 Histopathological characteristics based on the distribution of metastatic lymph nodes.

	Patients with pN0 (n=83)		**Patients with pN+ (n=107)**				**P-value (positive vs. negative UM nodes)**
			Positive UM nodes (n=27)		**Negative UM nodes (n=80)**		
Siewert classification							0.129
No malignancy	17	20.2%	0	-	2	2.5%	
Type 1	24	28.6%	14	51.9%	25	31.3%	
Type 2	42	50.0%	13	48.1%	53	66.3%	
pT-stage							0.614
T0	17	20.5%	0	-	2	2.5%	
Tis	1	1.2%	0	-	0	-	
T1	13	15.7%	4	14.8%	7	8.8%	
T2	21	25.3%	2	7.4%	13	16.3%	
T3	31	37.3%	20	74.1%	56	70.0%	
T4a	0	-	1	3.7%	2	2.5%	
pN-stage							<0.001
N0	83	100%	0	-	0	-	
N1	0	-	8	29.6%	44	55.0%	
N2	0	-	8	29.6%	29	36.3%	
N3	0	-	11	40.7%	7	8.8%	
pM-stage							0.062
M0	83	100%	25	92.6%	80	100%	
M1	0	-	2	7.4%	0	-	
Total harvested lymph nodes							0.609
(median, IQR)	20.0	14 – 29	25.0	18 – 30	22.0	18 – 30	
Total positive lymph nodes							0.001
(median, IQR)	0	0 – 0	5.0	2 – 11	2.0	1 – 4	
Completeness of resection							0.099
R0	82	98.8%	20	74.1%	70	87.5%	
R1	1	1.2%	7	25.9%	10	12.5%	

UM = upper mediastinal, IQR = interquartile range

Survival

Median follow-up in surviving patients was 49.6 months (IQR 35.1 – 71.9). Overall disease-free survival and 5-year survival in the entire cohort were 27.2 and 38% months, respectively. 34.9% of patients without nodal involvement developed recurrent disease, compared to 65.2% of pN+/UM- patients and 83.3% of UM+ patients (p<0.001). The median disease-free survival of patients with N0-disease was not yet reached. Patients with pN+/UM- had a median disease-free survival of 19.8 months, whereas patients with UM+ had a median disease-free survival of 12.3 months (P=0.004, Figure 2A). With respect to overall survival, patients without nodal involvement had a 5-year survival of 63%, patients with pN+/UM- 29% and patients with UM+ 14% (p=0.031, Figure 2B). The 5-year survival rates of patients with a positive node at each specific nodal station were as follows: paratracheal 16.7% (n=6), aortapulmonary window 100.0% (n=1), subcarinal 14.6% (n=20), paraesophageal 25.3% (n=40), paracardial 24.4% (n=25), lesser curvature 24.7% (n=79).

Subgroup analyses were performed in patients treated without neoadjuvant therapy, perioperative chemotherapy and neoadjuvant chemoradiation. In all subgroups, patients with upper mediastinal nodal involved had poor overall survival (Supplementary File 1).

Table 3 Distribution of metastatic lymph nodes depending on neoadjuvant therapy

		Patients with pN+ (n=107)					
	Patients with pN0 (n=83)	**Positive UM nodes (n=27)**		**Negative UM nodes (n=80)**			**P value**
Neoadjuvant therapy							0.004
None	9	19.8%	9	18.8%	29	60.4%	
Chemotherapy	36	46.2%	9	11.5%	33	42.3%	
Chemoradiation	36	57.1%	9	14.3%	18	28.6%	
Radiotherapy	2	100%	-		-		

UM = upper mediastinal

Prognostic factors

Univariable analysis identified a higher pT-stage (p<0.001), irradical resection (R1, p<0.001), UM+ (p<0.001) and total positive lymph nodes (p<0.001) as prognostic factors associated with a worse overall survival (Table 4). On multivariable analysis, a pT3/T4a tumor and UM+ remained as independent prognostic factors for overall survival.

Table 4 Univariable and multivariable COX regression analysis of prognostic factors for overall survival.

	Univariable			**Multivariable**		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age	1.002	0.980 – 1.024	0.862	-		
Male gender	1.047	0.622 – 1.761	0.864	-		
BMI	1.002	0.951 – 1.055	0.944	-		
Neoadjuvant therapy				-		
None	Reference					
Chemotherapy	0.950	0.594 – 1.518	0.950			
Chemoradiation	0.908	0.532 - 1.549	0.908			
Siewert classification			0.404	-		
Type 1	Reference					
Type 2	1.198	0.783 – 1.833				
pT-stage			<0.001			
T0	Reference			Reference		
T1	3.323	0.914 – 12.074		2.214	0.598 – 8.202	0.234
T2	2.633	0.743 – 9.333		2.264	0.578 – 7.391	0.264
T3	6.777	2.133 – 21.532		3.403	1.424 – 11.322	0.046
T4a	32.755	8.027 - 133.579		7.746	1.424 – 42.136	0.018
Radicality of resection			<0.001			
R0	Reference			Reference		
R1	3.206	1.938 – 5.305		1.516	0.808 – 2.844	0.195
Location lymph nodes			<0.001			
No nodal involvement	Reference			Reference		
N+ and negative UM nodes	2.516	1.571 – 4.029		1.653	0.961 – 2.843	0.069
N+ and positive UM nodes	4.419	2.467 – 7.914		2.274	1.021 – 5.064	0.044
Total positive lymph nodes	1.127	1.084 – 1.171	<0.001	1.033	0.956 – 1.107	0.348

BMI = body mass index, UM = upper mediastinal, HR = Hazard Ratio, CI = Confidence Interval

DISCUSSION

In this study, the location of metastatic lymph nodes was demonstrated to be important for the prognosis of patients with an adenocarcinoma of the gastroesophageal junction. Especially patients with positive nodes in the upper mediastinum are likely to develop recurrent disease and consequently have a poor disease-free and overall survival. With neoadjuvant therapy either consisting of chemotherapy or chemoradiation, a lower number of patients with N+ disease and UM nodal involvement was seen. Nevertheless, overall survival in these patients remained poor in case of metastatic UM nodes.

Lymph node status is considered to be an important predictor of outcome in adenocarcinoma of the GEJ. Due to the complex network of lymphatic vessels surrounding the esophagus, a longitudinal drainage pattern is present[11]. Tumor can metastasize along the esophagus to the upper mediastinum and even cervical, as well as downward to the upper abdomen[8, 12]. Especially GEJ tumors, located at the border of the thorax and abdomen, can metastasize to both sides of the diaphragm. The highest incidence of metastatic lymph nodes in patients with GEJ tumor is near the left gastric artery and paraesophageal. A previous study on GEJ adenocarcinoma reported perigastric node involvement in 45% and paraesophageal node involvement in 25% of patients[12], which is very much comparable to the current study where 43.8% of patients had lymph nodes metastasis at the lesser curvature and 22.9% paraesophageal. However, the presence and importance of upper mediastinal nodal involvement is not yet fully understood. In this study we found that 14.1% of patients had metastatic UM nodes which clearly demonstrates that this relevant subgroup needs to be evaluated more thoroughly.

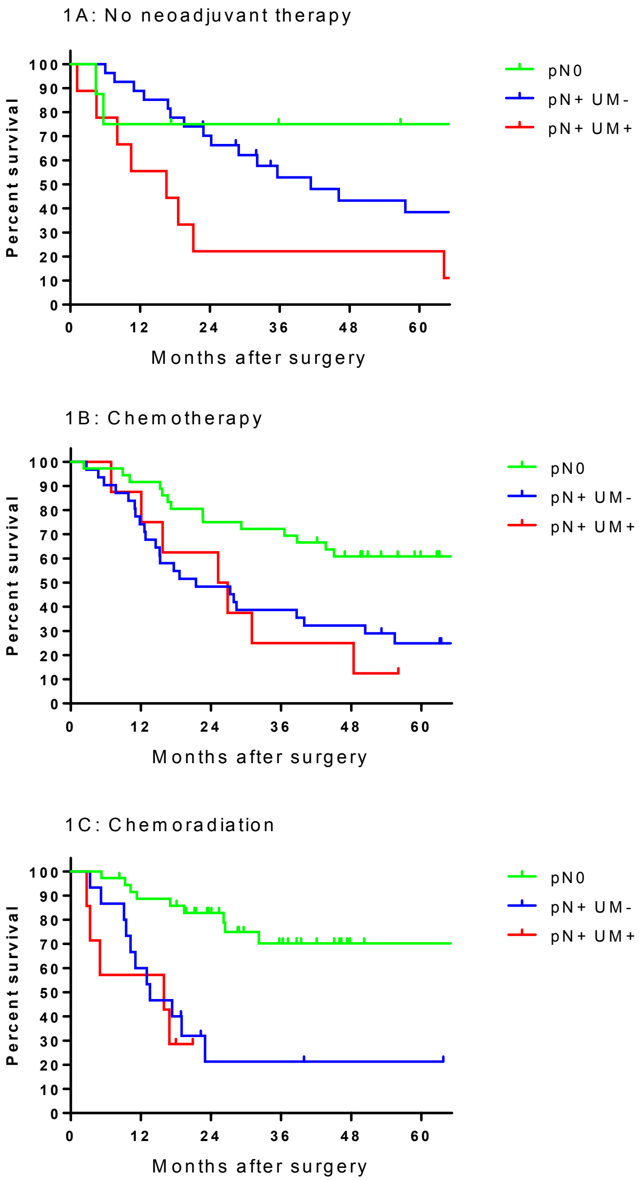
The location of metastatic lymph nodes is not considered as a prognostic factor in the current TNM staging system. In the previous edition cervical and truncal nodes were taken into account as a separate group with M1a disease. In the current edition (TNM 7) these nodes are classified as regional and only the number of positive lymph nodes is considered to be relevant for prognosis of the patient. However, it has been demonstrated before that also the distribution of metastatic lymph nodes is important for overall survival. For example, previous studies have demonstrated that patients with metastatic nodes on both sides of the diaphragm have worse overall survival[13, 14]. Furthermore, a recent study described the prognostic significance of metastatic lymph nodes in the proximal mediastinum, i.e. in their study a 5-year survival of 24.4% was found in patients with positive nodes in the proximal mediastinum and even 0.0% if the patient also had positive nodes at the celiac trunc[15]. These findings are in accordance with the current study in which patients with UM+ had a poor 5-year survival of 14%. Although patients with UM+ had significantly higher pN-stage compared to patients with UM-, which could indicate that UM+ expresses more advanced disease in these patients, multivariable analysis confirmed upper mediastinal node involvement to be a predictive factor for overall survival. This clearly demonstrates that, besides well-known factors such as tumor infiltration depth, radicality of resection and number of positive lymph nodes, the distribution pattern of metastatic lymph nodes is also important for patient prognosis. To this extent, a number of authors proposed a revised classification system for esophageal and GEJ adenocarcinoma which incorporates the location of metastatic lymph nodes. Although these studies demonstrate a greater prognostic stratification than the current TNM edition, they need validation in large independent datasets[13, 16].

The current TNM staging system used data from thirteen institutions and three continents to evaluate patients who underwent esophagectomy without neoadjuvant therapy. However, this staging system might be inadequate to predict prognosis in the current era of multimodality treatment. Nowadays most patients are treated with neoadjuvant therapy and a complete pathological response with complete lymph node clearance is a major determinant of outcome and might predict survival even better[17, 18]. In several studies, the impact of neoadjuvant therapy on the number of metastatic lymph nodes has been described[17, 19]. These findings are confirmed in the present study showing a difference in the number of metastatic lymph nodes as well as in the distribution pattern of nodes between patients treated with and without neoadjuvant therapy. N+ disease on histopathology was found in 43% of patients treated with neoadjuvant chemoradiation and in 79% of patients treated without neoadjuvant therapy. In addition, we found that only 11.5% of patients treated with neoadjuvant chemotherapy had positive upper mediastinal nodes compared to 18.4% of patients treated without neoadjuvant therapy. This suggests that neoadjuvant therapy might impact the number of metastatic nodes and the distribution pattern of these nodes. Nevertheless, if upper mediastinal node involvement is still present after neoadjuvant therapy it is associated with a dismal outcome. This indicates the clinical importance of a new staging system that incorporates the current use of neoadjuvant therapy and as well as the location of metastatic lymph nodes as a prognostic factor.

This study has some limitations that need to be addressed. First of all, this is a retrospective study which consequently leads to selection bias. Secondly, while we demonstrated an impressive reduction of N+ disease after neoadjuvant therapy, the reduction in UM positive lymph nodes after chemoradiation was less striking. In these patients it is important to know whether the lymph nodes were within the radiation field. Unfortunately, this information was not available in this retrospective series. Lastly, the lymph nodes paratracheal, subcarinal, para-esophageal and near the left gastric artery were marked during surgery for postoperative analysis. However, the determination of the other stations was done by the pathologist. Since all abdominal stations are very close to each other, it is difficult for a pathologist to distinguish between the abdominal stations after en-bloc removal of these lymph nodes. Therefore, we have chosen to combine the abdominal lymph nodes at the lesser curvature/left gastric artery to avoid inaccuracy of each specific station separately.

In conclusion, in addition to tumor infiltration depth, number of positive lymph nodes and radicality of resection, the location of metastatic lymph nodes in patients with an adenocarcinoma of the GEJ is predictive of overall survival and should be used as a prognostic factor in future staging systems.

Supplementary file 1 Survival curves by the Kaplan Meijer method depending on location of metastatic nodes in A: patients treated without neoadjuvant therapy, B: patients treated with neoadjuvant chemotherapy, C: patients treated with neoadjuvant chemoradiation.



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Chapter 11

Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent.

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***Annals of Surgical Oncology*,**
2015 Dec; 22 *Suppl* 3:S1292-300

ABSTRACT

Background
Strategies for treatment of recurrence after initial curative esophagectomy are increasingly being recognized. The aim of this study was to identify prognostic factors that affect survival in patients with recurrence and to evaluate treatment strategies.

Methods
A prospective database (2003-2013) was used to collect consecutive patients with esophageal carcinoma treated with initial curative esophagectomy. Locations, symptoms, and treatment of recurrence were registered. Post-recurrence survival was defined as time between the first recurrence and death or last follow-up.

Results
Of the 335 selected patients, 171 (51%) developed recurrence. Multivariable analysis identified distant recurrence as opposed to locoregional recurrence (hazard ratio [HR] 2.15, 95% confidence interval [CI] 1.27-3.65; p=0.005), >3 recurrent locations (HR 2.42, 95% CI 1.34-4.34; p=0.003) and treatment (HR 0.29, 95% CI 0.20-0.44; p<0.001) as independent prognostic factors associated with post-recurrence survival. Primary tumor characteristics including neoadjuvant therapy, histological type, pTN-stage, and radicality did not independently influence post-recurrence survival. Treatment was initiated in 62 patients (37%) and included chemotherapy, radiotherapy, and/or surgery. Median post-recurrence survival of all patients was 3.0 months (range 0-112). In total 6 patients (4%) are still disease free following treatment indicating cure.

Conclusion
In patients treated for esophageal cancer at curative intent, distant recurrence and >3 recurrent locations are independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics. Although survival after recurrence is poor, treatment can prolong survival and in selected patients even lead to cure.

INTRODUCTION

Esophageal carcinoma is the sixth leading cause of cancer-related mortality worldwide and the incidence is rapidly increasing[1, 2]. Multimodality treatment combining neoadjuvant chemo(radio)therapy and surgical resection has improved the prognosis for resectable non-metastatic disease[3]. However, more than half of the patients develop recurrence within 3 years after treatment with curative intent[4-7]. The prognosis of recurrent esophageal cancer is poor with a median survival after developing a recurrence of 3 to 10 months[4, 8-10]. Therefore, detecting prognostic factors affecting post-recurrence survival and determining effectiveness of treatment strategies for recurrence are of high importance. Treatment can be attempted in a fair number of patients with recurrent disease and may include chemotherapy, radiotherapy, surgery, or a combination[9, 11, 12]. However, the optimal treatment strategy for esophageal cancer patients with recurrent disease is not yet established and patients respond differently to treatment with a wide range in long-term survival[12].

The aim of this study was to investigate prognostic factors that affect survival in patients diagnosed with recurrent disease after prior esophagectomy with curative intent for esophageal carcinoma. A second aim was to evaluate the different treatment strategies applied.

PATIENTS AND METHODS

Patients

In this single-center cohort study patients were selected from a prospectively assembled database at the University Medical Center Utrecht, The Netherlands. Between October 2003 and December 2013, 379 consecutive patients were planned for esophagectomy with curative intent for esophageal carcinoma. Patients with an unresectable tumor (cT4b) or metastatic disease (M1) detected intraoperatively were excluded (n=22). Patients deceased within 90 days after surgery or during hospitalization, were also excluded (n=22). Of the remaining 335 patients, 171 were diagnosed with recurrent disease and were included in this study. Histopathological staging was performed according to the TNM-7 staging system of the American Joint Committee on Cancer (AJCC)[13]. All patients were discussed at a multidisciplinary tumor board meeting preoperatively, postoperatively and after developing recurrent disease. Institutional Review Board approval was obtained and the informed consent requirement was waived for this study.

Treatment

Eligible patients with locally advanced disease (cT≥2 or cN+) and without clinical evidence of metastatic disease (cM0) received either perioperative chemotherapy or neoadjuvant chemoradiation according to the Dutch guidelines. Eligible patients were >18 years of age, had a WHO performance status ≤2, and did not lose >10% of their body weight. Before 1 June 2012, the standard treatment for patients with esophageal carcinoma consisted of perioperative chemotherapy (epirubicin, cisplatinum and 5-fluorouracil)[14] and, after that, patients underwent neoadjuvant chemoradiation (carboplatin AUC2 and paclitaxel 50 mg/m2 weekly during 5 weeks concomitant with 41.4 Gy (23x 1.8 Gy)[3]. Before 2008 neoadjuvant therapy was not a part of the standard protocol and most patients were operated on without neoadjuvant therapy. Patients not eligible for neoadjuvant treatment were treated with surgical esophageal resection alone. After esophagectomy with en bloc lymphadenectomy, all patients underwent gastric tube reconstruction with a cervical anastomosis.

Histopathological analysis

The resected specimens were reviewed by experienced pathologists in accordance with the TNM-7 staging system of the AJCC[13]. The resection margins were evaluated using the definitions of the College of American Pathologists[15, 16].

Follow-up and definition of recurrence

After esophagectomy, patients were followed at the outpatient clinic with an interval of 3 months in the first year, 6 months in the second year and 12 months thereafter until discharge after 5 years of follow-up. Follow-up consisted of medical history and physical examination. In case of clinical suspicion of tumor recurrence, diagnostic imaging was performed. Recurrence was confirmed by histopathological biopsy or clinical follow-up. Only the initial number and sites of recurrences were evaluated. The pattern of recurrence was classified as locoregional, distant or a combination of both. Recurrences at the anastomotic site or within the area of previous resection and nodal clearance in the mediastinum or upper abdomen were classified as locoregional recurrence. Distant recurrence was defined as recurrence in distant organs, pleura or peritoneal cavity, or distant lymph nodes. Disease-free survival was defined as time between day of surgery and day of recurrent disease. Post-recurrence survival was defined as the time between the first recurrence and death or last follow-up.

Treatment of recurrence

Treatment for recurrent disease was discussed at a multidisciplinary tumor board meeting and recommended if the patient was eligible. General considerations regarding eligibility included patient condition, location of recurrences, prior toxicity from chemo- or radiotherapy, and patient's wish. Treatment consisted of chemotherapy, radiotherapy and/or surgery focused on tumor reduction. Radiotherapy focused on tumor reduction was defined as radiotherapy with a radiation dose >30 Gy, excluding palliative radiotherapy for bone metastases. In all other cases, patients were treated with best supportive care.

Statistical analysis

To assess prognostic factors for post-recurrence survival univariable and multivariable analyses by means of Cox proportional hazard models were used, providing hazard ratios (HRs) with 95% confidence intervals (CIs). All variables with $p<0.20$ in univariable analysis were entered in a multivariable analysis. Kaplan-Meier survival curves were constructed for the prognostic factors that remained significantly associated with post-recurrence survival in multivariable analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 21 for Windows.

RESULTS

Patients characteristics

The median follow-up of the 335 consecutive patients treated with esophagectomy in the study period was 22.0 months (range 2-135). Of all patients, 171 (51%) developed recurrent disease and those patients were included in this study. The clinical and histopathological characteristics of these 171 patients are shown in Table 1. Mean age was 63 years (SD 8.8) and most patients were male (n=131, 77%). Perioperative chemotherapy was administered in 63 patients (37%) and neoadjuvant chemoradiation in 35 (21%). The surgical procedure consisted of a transthoracic approach in 132 patients (77%) and a transhiatal approach in the remaining 39 patients (23%). Tumor histology was adenocarcinoma in 136 patients (80%). Histopathology revealed ≥pT3 (n=129, 75%) and pN+ disease (n=123, 72%) in the majority of patients. Of all patients that developed a recurrence, 139 (81%) underwent a microscopically radical (R0) resection.

Pattern of recurrence

Median time to recurrence was 9.0 months (range 1-86), and 164 patients (96%) developed recurrence within 3 years after surgery. The most common presenting symptoms were pain (n=38, 22%), malaise (n=23, 14%), dysphagia (n=21, 12%) and anorexia (n=21, 12%). The diagnosis of recurrent disease was based on computed tomography (CT) findings in 118 patients (69%), whereas in other patients the diagnosis was made with either endoscopic ultrasound upper (EUS), upper endoscopy, positron emission tomography (PET) or magnetic resonance imaging (MRI). The type of recurrence and the number of locations are presented in Table 2. Distant recurrence was the most common type of recurrent disease (n=76, 44%) and the liver was the most commonly affected site (n=50, 15%).

Factors affecting post-recurrence survival

Median post-recurrence survival was 3.0 months (range 0-112). The overall 1- and 2-year post-recurrence survival rates were 17% and 7%. Nodal status, type of recurrence, number of locations, time to recurrence and treatment of recurrence were significantly associated with post-recurrence survival in univariable analysis (Table 3, Figure 1). In multivariable analysis, distant recurrence (HR 2.15, 95% CI 1.27-3.65; p=0.005), >3 recurrent tumor locations (HR 2.42, 95% CI 1.34-4.34; p=0.003) and treatment (HR 0.29, 95% CI 0.20-0.44; p<0.001) were identified as independent

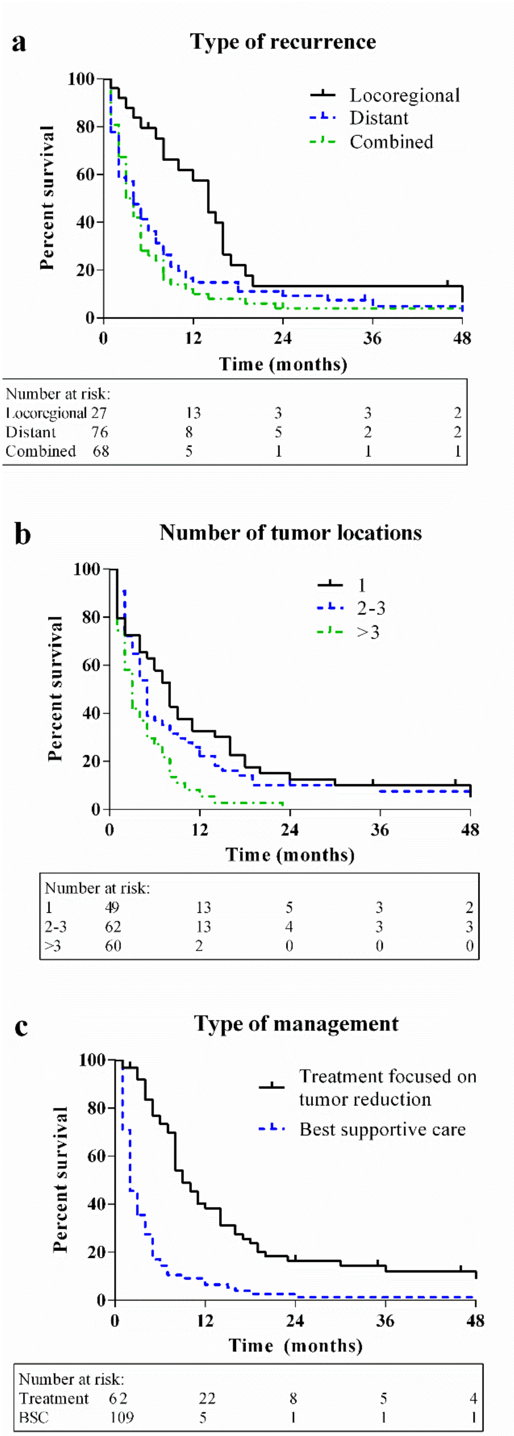

Figure 1 A: Type of recurrence, B: number of tumor locations, and C: type of management were identified as independent prognostic variables for post-recurrence survival in 171 patients with recurrence disease after curative esophagectomy. Survival curves were plotted using the Kaplan-Meier method.

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Table 1 Clinical and histopathological characteristics of 171 patients with recurrent disease after esophagectomy with curative intent.

	Recurrence Total = 171 n	(%)
Gender		
Male	131	(77)
Female	40	(23)
Age, years [mean ±SD]	63	±8.8
ASA score		
1	49	(29)
2	95	(56)
≥3	27	(16)
Neoadjuvant therapy		
No neoadjuvant therapy	72	(42)
Chemotherapy	63	(37)
Radiotherapy	1	(1)
Chemoradiation	35	(21)
Surgical approach		
Transthoracic	132	(77)
Transhiatal	39	(23)
Adjuvant therapy		
No adjuvant therapy	137	(80)
Chemotherapy	34	(20)
Histological type		
Adenocarcinoma	136	(80)
Squamous cell carcinoma	34	(20)
Other	1	(<1)
pT stage		
T0	9	(5)
T1	16	(9)
T2	17	(10)
T3	121	(71)
T4	8	(5)
pN stage		
N0	48	(28)
N1	49	(29)
N2	47	(28)
N3	27	(16)
Number of harvested lymph nodes (median [range])		
Radicality	20	[2-80]
R0	139	(81)
R1	32	(19)

prognostic factors associated with post-recurrence survival (Table 3). The median post-recurrence survival of patients with distant and locoregional recurrence was 2.0 months and 12.0 months respectively, and for patients with >3 recurrent tumor locations and a solitary recurrence 2.0 months and 6.0 months respectively. Patients who received treatment had a median post-recurrence survival of 9.0 months as compared to 2.0 months in patients treated with best supportive care. Primary tumor characteristics including neoadjuvant therapy, histological type, pTN-stage, and radicality of resection did not independently influence post-recurrence survival in multivariable analysis.

Treatment of recurrence

Best supportive care was given to 109 patients (63%). Patients receiving best supportive care were mainly either not eligible for treatment due to a poor performance status (n=63, 37%) or refused treatment (n=29, 17%). Some patients were not eligible due to prior toxicity of the neoadjuvant treatment regimen (n=4, 4%) or due to tumor location (n=4, 4%). Treatment focused on tumor reduction was applied in 62 patients (37%) (Table 2). Patients with locoregional recurrence (n=19, 70%) and solitary recurrence (n=24, 49%) more often received treatment focused on reduction compared with those with distant recurrence (26, 34%) and >3 recurrent tumor locations (n=14, 23%). Different chemotherapy regimens were administered in 41 patients; most patients received a combination of epirubicin, cisplatin and capecitabine (n=20, 48%). After treatment with chemotherapy only, 2 patients (5%) clinically showed a complete tumor regression. One patient had a solitary metastasis in the liver and the other patient had a solitary locoregional recurrence in the gastric conduit and truncal node. Both patients were alive at last follow-up (35 and 112 months after diagnosis of recurrence). In 13 of 171 patients (8%) surgical resection of the recurrence was performed (Table 4). Most of these patients had a solitary recurrence (n=9, 69%) at a distant location (n=11, 85%). The surgical resections are outlined in table 4, 5 patients (38%) underwent metastasectomy of a brain lesion. Median post-recurrence survival in patients who underwent resection was 11 months (95% CI 4.5-17.5). In 11 of 13 patients (85%) the resection was performed with curative intent. Of these patients, 4 of 11 (36%) were still alive at last follow-up with a follow-up of 5, 46, 53, and 87 months after the diagnosis of their recurrence, whereas the remaining 7 patients (64%) deceased due to disease progression.

Table 2 Location and treatment recurrence of 171 patients with recurrent disease after esophagectomy with curative intent.

	Recurrence Total = 171	
	n	**(%)**
Type of recurrence		
Locoregional	27	(16)
Distant	76	(44)
Combined	68	(40)
Location distant recurrence		
Liver	50	(15)
Lung	41	(13)
Abdominal lymph nodes	40	(12)
Retroperitoneal	40	(12)
Bone	30	(9)
Other	123	(38)
Number of locations with recurrence		
1	49	(29)
2-3	62	(36)
>3	60	(35)
Type of management		
Treatment focused on tumor reduction	62	(37)
Chemotherapy	24	(14)
Radiotherapy	11	(6)
Chemoradiation	13	(8)
Surgery	5	(3)
Surgery + chemotherapy	4	(2)
Surgery + radiotherapy	4	(2)
Other	1	(1)
Best supportive care	109	(63)
Condition	63	(37)
Patient wish	29	(17)
Toxicity	4	(2)
Location	4	(2)
Other	6	(4)
Unknown	3	(2)

Table 3 Univariable and multivariable analysis of potential prognostic factors for survival after diagnosis of recurrent esophageal carcinoma.

	HR	95% CI	p-value*	HR	95% CI	p-value**
Age (years)	1.02	1.00-1.04	0.055	1.00	0.99-1.02	0.670
Neoadjuvant therapy						
None	Reference	-	-	Reference	-	-
Chemotherapy	1.39	0.98-1.99	0.067	1.02	0.70-1.49	0.936
Radiotherapy	3.45	0.47-25.23	0.222	7.85	0.99-62.54	0.052
Chemoradiation	1.26	0.82-1.94	0.297	0.84	0.50-1.41	0.512
Histological type						
Adenocarcinoma	Reference	-	-			
Squamous cell carcinoma	1.24	0.84-1.84	0.272			
Other	1.10	0.15-7.93	0.922			
pT stage						
T0	Reference	-	-	Reference	-	-
T1-2	0.47	0.21-1.06	0.067	0.60	0.25-1.41	0.243
T3-4	0.70	0.34-1.45	0.341	0.78	0.34-1.76	0.545
pN stage						
N0	Reference	-	-	Reference	-	-
N1	1.80	1.18-2.75	0.007	1.50	0.95-2..37	0.080
N2-3	1.35	0.91-1.99	0.131	1.10	0.70-1.73	0.689
Radicality						
R0	Reference	-	-			
R1	1.20	0.81-1.77	0.363			
Type of recurrence						
Locoregional	Reference	-	-	Reference	-	-
Distant	2.10	1.30-3.41	0.003	2.15	1.27-3.65	0.005
Combined	2.54	1.55-4.16	<0.001	1.58	0.89-2.81	0.120
Number of locations						
1	Reference	-	-	Reference	-	-
2-3	1.21	0.81-1.79	0.357	1.30	0.83-2.00	0.250
>3	2.20	1.46-3.32	<0.001	2.42	1.34-4.34	0.003
Time to recurrence (months)	0.98	0.96-1.00	0.013	0.99	0.98-1.01	0.263
Treatment of recurrence						
Best supportive care	Reference	-	-	Reference	-	-
Treatment focused on tumor reduction	0.27	0.19-0.38	<0.001	0.29	0.20-0.44	<0.001

Analysis was performed using Cox regression model. * univariable analysis, ** multivariable analysis. Bold values indicates statistically significant (e.g. p<0.05). All variables with p<0.2 from univariable were used for multivariate analysis. HR: hazard ratio, CI: confidence interval.

DISCUSSION

In this single-center cohort study, 171 patients with recurrent disease after treatment with curative intent for esophageal carcinoma were analyzed and factors affecting post-recurrence survival were evaluated. Distant recurrence and more than 3 recurrent locations were identified as independent prognostic factors associated with a worse post-recurrence survival, irrespective of primary tumor characteristics. Furthermore, treatment focused on tumor reduction as opposed to best supportive care prolonged survival in eligible patients and a selected group of patients were treated curatively.

This study confirms the poor prognosis of recurrent esophageal cancer reported in other series with a median post-recurrence survival of 3.0 months and a 2-year survival rate of only 7%[4, 8-10]. Hence, understanding of the prognostic factors influencing survival is important to identify patients who could have an improved post-recurrence survival by selecting them for the appropriate treatment. In accordance with the literature, distant recurrence was associated with a worse survival in this study reflecting aggressive tumor biology[6, 12, 17]. Furthermore, this study showed that patients with > 3 recurrent tumor locations have a worse post-recurrence survival compared to those with less involved locations, which could also be explained by the more aggressive behaviour of multiple recurrences. The survival of patients with > 3 recurrent locations was extremely poor, with a median survival of 2.0 months after the diagnosis of recurrence as compared to 6.0 months in patients with a solitary recurrence. The majority of patients had a poor clinical condition at the time of diagnosis of recurrence and were therefore considered ineligible for treatment focused on tumor reduction. The patients that did undergo treatment had a significantly prolonged survival, which is likely explained by a combination of appropriate patient selection and treatment effectiveness.

As has been reported in previous studies, all different treatment strategies resulted in a prolonged survival in the current study[4, 9, 18]. This finding suggests that all patients with recurrent disease should be stimulated to undergo treatment if the condition of the patients allows it. The median post-recurrence survival in the treated group was 8.5 months compared to 2.0 months for those who were treated with best supportive care. It needs to be acknowledged that the majority of patients who received best supportive care were not eligible for therapy, causing bias through selection-by-indication in this comparison. Nonetheless, most patients that were not eligible had advanced disease (i.e. distant recurrence or > 3 recurrent locations), which reflects high dependency of the patient's condition on the site and number of recurrent tumors.

Patients were treated with various therapies of which chemotherapy was the most commonly applied. The benefit of a surgical resection of recurrent esophageal carcinoma is not yet completely elucidated. A few reports showed improved survival after surgical resection[11, 19, 20]. However, in most studies the resection was combined with either chemo- or radiotherapy and performed only in a small number of patients. Also in this study a small group of patients (n=13) underwent resection of their recurrence. The majority (n=9) had an oligometastasis. Patients with oligometastases represent a special tumor behaviour that is likely to gain from local control. In other types of cancer, the current literature shows also a survival benefit with long disease free survival from local control with surgery for patients with oligometastases[21, 22]. Importantly, 4 patients had complete tumor remission after the resection and were still alive at last follow up. Other studies also reported long-term survival after treatment of recurrent disease for esophageal carcinoma[11, 23-25]. These findings suggest that a favourable outcome can be expected after surgical resection in a selected patient group, especially for those with solitary or localized recurrence of esophageal cancer. Although treatment of recurrence resulted in prolonged survival, the majority of patients (63%) received best supportive care. This is in contrast with some other studies where the proportion of patients receiving best supportive care ranged from 12 to 44%[9, 11, 17, 26, 27]. An explanation for the high percentage of best supportive care in this cohort could lie in the follow-up strategy. The current follow-up strategy is based on the existing literature showing that routine diagnostic imaging is of no benefit with regard to survival and costs[28]. Furthermore, the consensus-based guidelines from the National Comprehensive Cancer Network also suggest to only perform diagnostic imaging when clinically indicated[29]. Hence, this follow up strategy is widely performed in the Netherlands. However, this strategy could have resulted in more advanced recurrent tumor stages at the moment of diagnosis. Since the patient's condition is largely determined by the number and site of recurrences, patients with multiple metastases are often not eligible for therapy. Therefore, the follow-up strategy may need revision according to the findings of the current study. In light of the new insights in the concept of oligometastases and the new combined treatment options we suggest to routinely perform a follow-up of patients with PET

Table 4 Characteristics, treatment, and survival of 13 patients treated with surgical resection

Case	Age (years)	Gender	pTNM stage	Time to recurrence (months)	Type of recurrence (months)	Location recurrence
1	56	Male	T3N2M0	11	Distant	Abdominal LN
2	44	Male	T3N2M0	3	Distant	Abdominal wall Inguinal cutane
3	74	Female	T4aN2M0	2	Distant	Upper leg subcutane Inguinal LN Abdominal wall Abdominal LN
4	67	Male	T3N2M0	8	Distant	Brain, lung, liver
5	53	Male	T0N0M0	21	Distant	Brain
6	77	Female	T3N0M0	14	Distant	Brain
7	75	Male	T1bN0M0	31	Distant	Lung
8	62	Female	T3N0M0	12	Distant	Brain
9	50	Male	T3N0M0	32	Distant	Vesiculae seminales
10	65	Male	T3N3M0	8	Combined	Quadriceps muscles Paraesophageal LN
11	56	Male	T2N0M0	13	Locoregional	Gastric conduit
12	65	Male	T1aN0M0	10	Distant	Liver
13	62	Male	T3N0M0	20	Distant	Brain

CT= chemotherapy, RT= radiotherapy, LN = lymph node for recurrent esophageal carcinoma.

Surgical intervention	Other treatments		Curative intent	Status	Survival after recurrence (months)
	CT	RT			
LN resection	No	No	Yes	Dead	53
Tumor resection Tumor resection	Yes	No	Yes	Dead	9
Tumor resection LN resection	No	Yes	No	Dead	4
Metastasectomy brain lesion	No	Yes	No	Dead	5
Metastasectomy brain lesion	No	Yes	Yes	Dead	7
Metastasectomy brain lesion	No	No	Yes	Dead	1
Partial pulmonary resection	No	No	Yes	Dead	18
Metastasectomy brain lesion	No	No	Yes	Dead	4
Excision vesiculae seminales	No	No	Yes	Dead	11
Metastasectomy quadriceps muscles	Yes	No	Yes	Alive	87
Resection gastric conduit with jejunal reconstruction	No	No	Yes	Alive	46
Hemihepatectomy	Yes	No	Yes	Alive	53
Metastasectomy brain lesion	No	Yes	Yes	Alive	5

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CT in the first 6-12 months following primary treatment[30]. Another explanation for the high ‘best supportive care’ rate could be the large proportion of patients (27%) who refused any form of treatment. In most other studies, only a fraction of patients did not receive treatment based on patient’s choice[26, 27, 31]. According to the results of the current study, eligible patients might be encouraged for treatment focused on tumor reduction to improve their survival. Unfortunately, no information on quality of life was obtained from patients that were treated for recurrence. Quality of life is of paramount importance in patients being treated with palliative intent.

In conclusion, survival after developing a recurrence after esophagectomy with curative intent is poor. Distant recurrence and > 3 recurrent locations were identified as independent factors associated with a worse survival, irrespective of primary tumor characteristics. Treatment focused on tumor reduction using various strategies contributed to a prolonged survival in all patients. Hence, focus is needed to improve patient selection for treatment in recurrent esophageal carcinoma. Additionally, in a small group of patients (4%) curative treatment of recurrent esophageal carcinoma appears possible.

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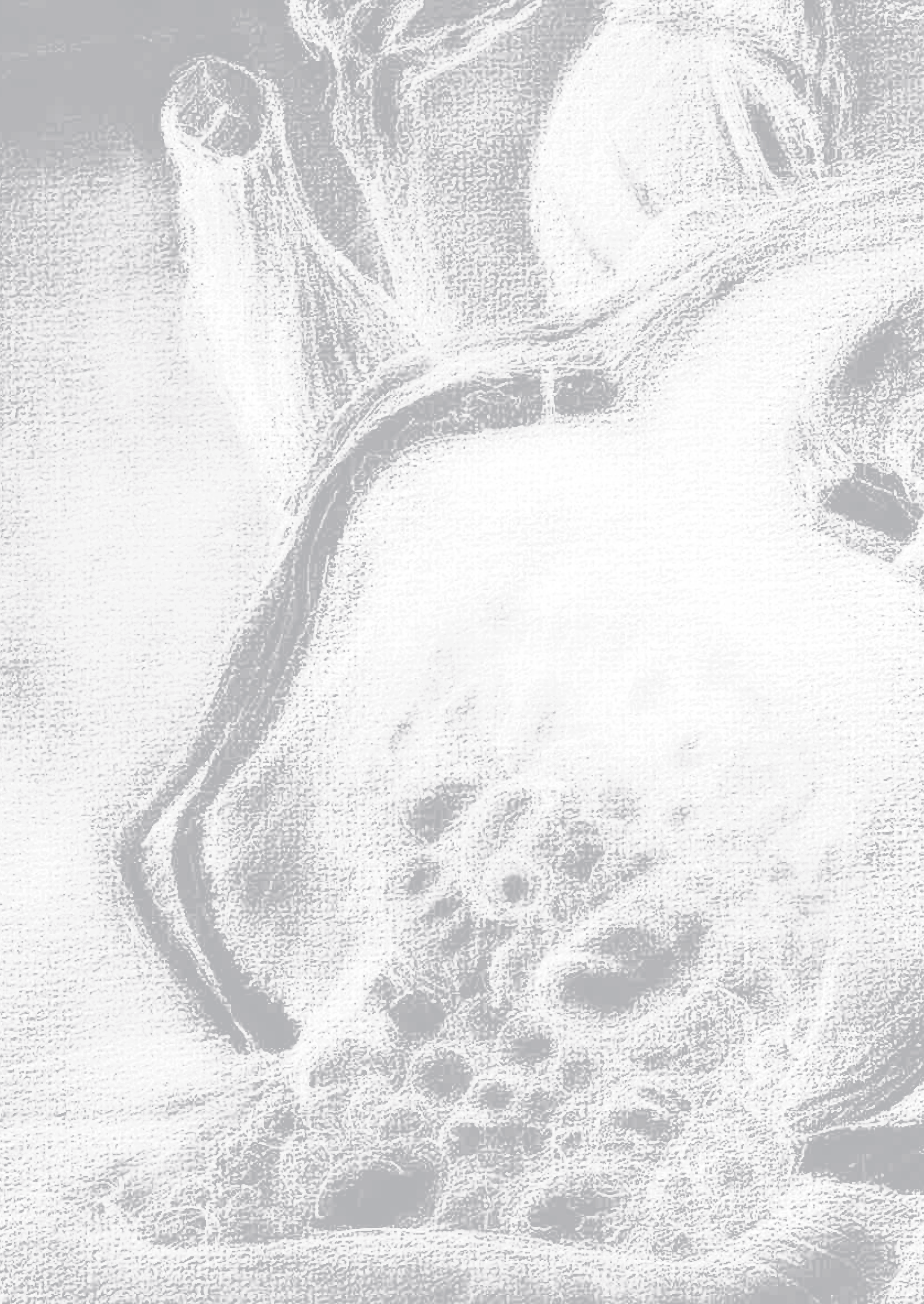
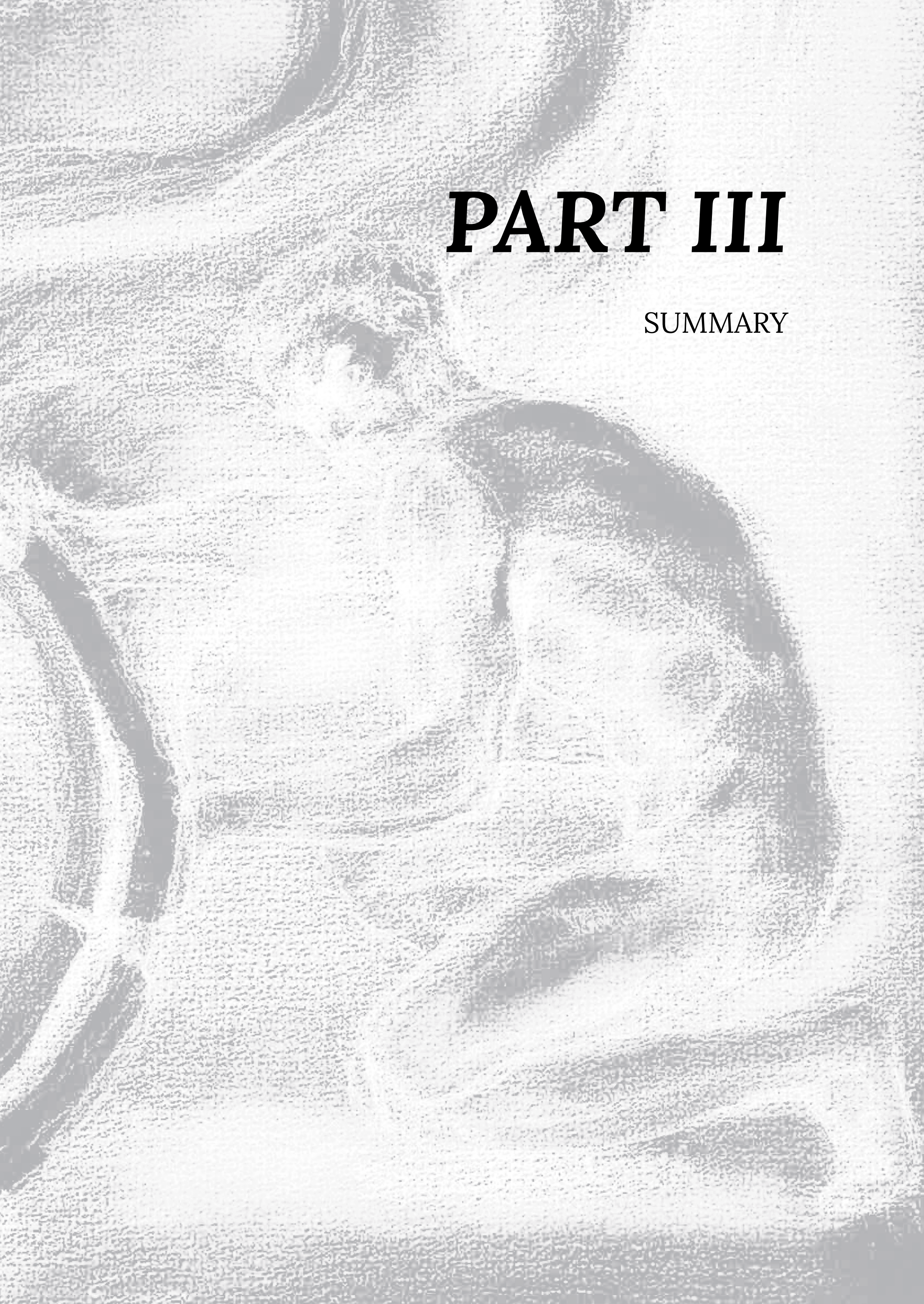


PART III

SUMMARY



Chapter 12

Summary

SUMMARY

Adenocarcinoma of the GEJ has seen a rapid increase in incidence over the last decades. Because of their borderline location between esophagus and stomach, the optimal management for these tumors is still an important subject for debate. Especially for the true cardiacarcinomas, i.e. type II tumors, there are still a lot of controversies regarding the optimal approach in neoadjuvant therapy and surgery. Although surgery is considered to be mandatory for curative treatment, postoperative complications are still a significant problem. Also, long-term survival in GEJ adenocarcinomas remains poor despite the increased use of multimodality treatments. The research presented in this thesis aims to evaluate current treatment strategies and to bring more insight in the optimal approach for GEJ adenocarcinomas. Secondly, important postoperative complications were evaluated. Also, prognostic factors for overall survival and recurrent disease were addressed.

PART I: STAGING AND TREATMENT

Clinical staging of adenocarcinoma of the GEJ determines the curative treatment regimen containing either neoadjuvant chemotherapy or chemoradiation followed by either gastrectomy or esophagectomy. To this extent, upper endoscopy and biopsy, endoscopic ultrasound (EUS) and thoraco-abdominal computed tomography (CT) are routinely used for pretreatment staging. However, the value of these diagnostic tools is a matter of debate. In **Chapter 2** these diagnostic modalities were evaluated for their accuracy in determining tumor localization according to Siewert and nodal status in a prospective cohort of 266 patients with GEJ adenocarcinoma. The overall accuracy for determining tumor localization was 73% for EUS and 61% for CT. The accuracy for the detection of a metastatic nodal station was 77% for EUS and 71% for CT. Especially upper mediastinal lymph nodes were accurately detected with rates between 80-92%, whereas accuracy was poor in peritumoral and abdominal nodes (rates between 50-80%). Despite the suboptimal accuracy for tumor localization, in only 3% of the patients the type of surgical treatment was adjusted intraoperatively. Moreover, a radical resection of 88% indicates good local control. It seems that EUS is superior to CT for determining tumor and lymph node location and plays an important role in treatment planning.

The optimal neoadjuvant approach for GEJ adenocarcinoma remains unclear. The aim of the study in **Chapter 3** was to assess the potential benefit of perioperative chemotherapy in a consecutive series of 196 patients with GEJ adenocarcinoma. Chemotherapy was administered in 124 patients (63%). Survival analyses between patients treated with and without neoadjuvant therapy failed to demonstrate any difference between the two groups regarding disease-free and overall survival. A pathological good response was achieved in 32 patients (34%), and in these patients the 5-year survival improved to 67% compared to 35% in patients without neoadjuvant therapy. However, the majority of patients were poor responders (n=81, 66%). These patients developed more recurrences than patients treated with surgery-alone and consequently had a poor 5-year survival of 21%. This indicates that perioperative chemotherapy is only beneficial in a subgroup of patients who respond well to chemotherapy. Therefore, it is important to find predictive biological or radiological markers that predict or assess chemotherapy sensitivity to alter the management if necessary.

In general type I tumors are treated with transthoracic esophagectomy and type III tumors with extended total gastrectomy. However, type II tumors are located at the anatomical GEJ and therefore literature does not provide conclusive insight in the optimal surgical approach. In **Chapter 4** histopathology and clinical course after esophagectomy and gastrectomy were evaluated in a consecutive series of 176 patients with type II tumors. In total 86% were treated with esophagectomy and 14% with gastrectomy. The overall survival in both groups was comparable and no significant differences were found regarding mortality, morbidity and disease recurrence. However, a positive circumferential resection margin was more common with gastrectomy (29% vs 11%). Furthermore, upper mediastinal nodal involvement was found in 11% of the patients and also more paraesophageal lymph nodes were found with esophagectomy. Based on these findings an esophagectomy might be preferable in type II tumors due to improved local control and appropriate lymphadenectomy of the upper mediastinal nodes.

The aim of the study in **Chapter 5** was to evaluate population-based treatment strategies for patients with GEJ adenocarcinoma and to compare oncological outcomes following esophagectomy and gastrectomy. In total 939 patients were treated with esophagectomy and 257 patients with gastrectomy. No differences were found regarding lymph node yield and R0-resection rates. The 5-year survival rate was 36% for esophagectomy and 33% for gastrectomy, which did not differ significantly. Also with multivariable survival analysis a significant difference between both procedures was not found. However, patients receiving neoadjuvant therapy prior to surgical resection experienced an improved survival compared to patients with surgery-alone despite the type of surgical approach. From this study we can conclude that neoadjuvant therapy has more impact on overall survival than surgical approach in GEJ adenocarcinomas.

Patients with esophageal cancer and severe comorbidities are often unsuitable for transthoracic esophagectomy. Transhiatal esophagectomy (THE), which avoids a thoracotomy, has been proven to reduce postoperative morbidity. The aim of the research in **Chapter 6** was to evaluate the postoperative course and survival in a consecutive series of 68 patients with significantly elevated risk for surgery who were offered THE. Of all patients, 37% were treated with neoadjuvant therapy. A postoperative complication occurred in 66% of the patients, with in most an anastomotic leakage (35%), pneumonia (34%) and/or atrial fibrillation (22%). Although 35% of the patients developed major complications requiring surgery or Intensive Care treatment, the in-hospital mortality (IHM) rate was only 3% and a 5-year survival of 36% was achieved. The low IHM and good 5-year survival reflects the benefit of taking the risk of this surgical procedure, even in this compromised group of patients.

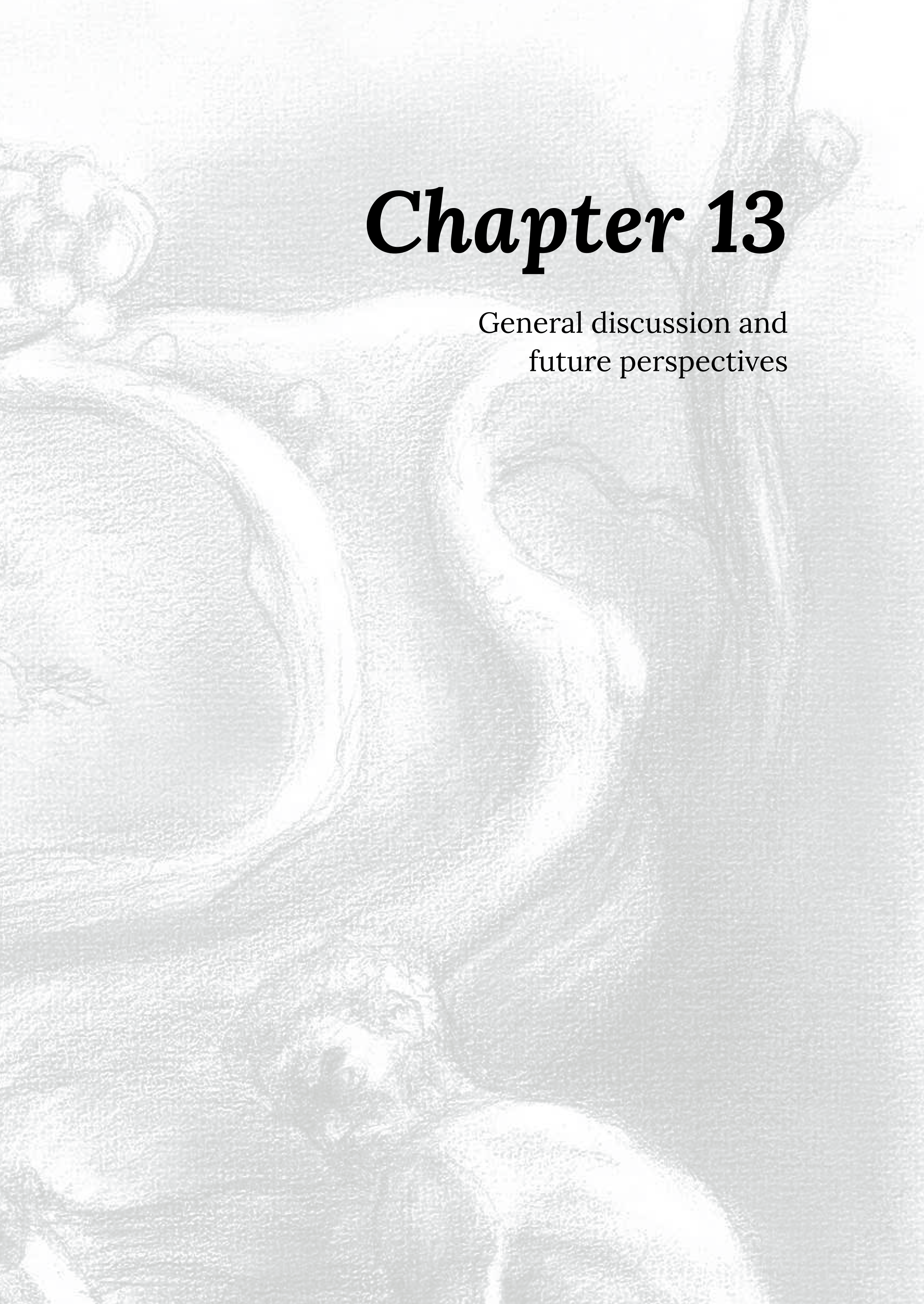
In **Chapter 7** the aim was to systematically review the current status and potential benefit of a minimally invasive approach in THE. A total of 4 comparative studies that compared laparoscopic versus open THE were included. In all 4 studies, a significantly lower median blood loss and shorter hospital stay was found with laparoscopy. No differences were found regarding operating time, postoperative morbidity, radicality, and lymph node retrieval. Based on the pioneer studies included in this review, a minimally invasive approach in THE was demonstrated to be safe and feasible with evidence of reduced blood loss and shorter hospital stays. However, level 1 evidence is lacking and further research is warranted to confirm these findings and also to evaluate long-term oncological outcomes.

PART II: POSTOPERATIVE COURSE AND SURVIVAL

Venous thromboembolic events (VTE), consisting of deep venous thrombosis and pulmonary embolism, can occur to up to 13.2% following esophagectomy for cancer. The use of intermittent pneumatic compression (IPC) as a prophylactic measure has not been investigated before in esophageal cancer surgery. In **Chapter 8** the development of postoperative VTE in 195 patients receiving IPC additionally to conventional thromboprophylaxis with LMWH was analyzed and compared with a historical cohort of 118 patients who received LMWH only. In the group of patients who received IPC 1.5% developed a symptomatic VTE compared to 6.8% in patient without IPC. Multivariable analysis identified IPC as the only independent prognostic factor correlated with reduced VTE rate. Therefore, we can conclude that mechanical IPC treatment in combination with standard thromboprophylaxis may be a viable and effective prophylaxis against VTE in patients undergoing esophagectomy for cancer.
Hiatal hernia (HH) is a long-term complication following esophagectomy and is becoming more relevant due to improvements in survival. The research in **Chapter 9** was conducted to evaluate the occurrence and clinical course of HH following open and minimally invasive esophagectomy (MIE) in 657 consecutive patients. HH occurred in 44 patients (7%) and was comparable after MIE and open esophagectomy (8% vs. 5%). Emergency surgery, which was necessary in 16 patients, resulted in a prolonged intensive care unit stay compared to elective surgery, which was performed in 10 symptomatic patients. All other patients with HH were treated conservatively. Hence, HH is a significant long-term complication after esophagectomy, occurring in a substantial proportion of the patients. Importantly, emergency surgery is associated with dismal outcomes and should be avoided.

The presence of metastatic lymph nodes is a strong prognostic factor of overall survival in patients with GEJ adenocarcinoma. However, uncertainties remain whether the location of metastatic lymph nodes is also correlated with outcome. In **Chapter 10** the importance of the location of metastatic lymph nodes in terms of survival in 199 patients with an adenocarcinoma of the GEJ was analyzed. Of all patients, nodal metastases were found in 116 patients (58%). Upper mediastinal nodal involvement (UM+) was seen in 27 patients (14.1%), whereas 80 patients (41.9%) had pN+ disease without metastatic UM nodes (UM-). Patients with UM+ developed more recurrences than patients without UM- and this correlated with a poor 5-year survival of 14% versus 29%. This demonstrates that also the location of metastatic lymph nodes in patients with an adenocarcinoma of the GEJ is predictive of overall survival and should be used as a prognostic factor in future staging systems.

The aim of the study in **Chapter 11** was to investigate prognostic factors that affect survival in 171 patients diagnosed with recurrent disease after curative esophagectomy. Distant recurrence as opposed to locoregional and more than 3 recurrent locations were independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics. Although a median post-recurrence survival of only 3 months demonstrates the extremely aggressive behavior of this disease, treatment can prolong survival and can even lead to cure in selected patients. This reflects the importance of careful disease and patient evaluation to determine whether treatment could be beneficial in the individual patient.



Chapter 13

General discussion and future perspectives

GENERAL DISCUSSION

A persistent debate regarding the optimal management of gastroesophageal junction (GEJ) tumors regarding neoadjuvant therapy and surgical approach exists amongst clinicians and scientists. The controversy is primarily focused on type II tumors. Type I tumors have frequent proximal esophageal extension and rare extension below the gastric cardia. Furthermore, the frequently mediastinal nodal involvement requires a thorough lymphadenectomy of the mediastinum. Therefore, these tumors are generally treated as esophageal cancer and treated correspondingly. Type III tumors, on the other hand, arise in the subcardia and often involve a significant part of the lesser curvature with lymph nodes that typically metastasize to perigastric regions. To provide for adequate tumor clearance, they can mostly be treated as gastric cancer with total gastrectomy. The focus of the debate centers on type II tumors, which are considered as true cardiacarcinomas. As these tumors are found at a late stage the 'epicenter' is often difficult to ascertain by endoscopy. The optimal management, including staging, the most appropriate type of neoadjuvant therapy and type of surgical approach need to be established. Further research is mandatory, given the increasing incidence of GEJ adenocarcinomas in western countries[1], and the presence of widely divergent 'evidence-based' treatments.

Staging

Diagnostic staging is important to elaborate an individualized treatment protocol for patients with GEJ adenocarcinoma. The overall accuracy of EUS and CT in determining Siewert classification and lymph node location was suboptimal as presented in Chapter 2. However, in only a small percent of patients a change in surgical strategy was needed with evidence of good local control. Nevertheless, the discrepancies between type I and type II, i.e. a substantial part of the histopathological type II tumors were preoperatively classified as type I, resulted in esophagectomy in most patients in our center. Also, misstaging type II and type III resulted in an irradical resection in 2 patients. To overcome this problem, a staging laparoscopy can be performed to determine the location of the tumor epicenter, to assess the length of tumor extent in the stomach and to decide whether the stomach is suitable for gastric-pull up reconstruction of the esophagus. Also, in gastric cancer there is compelling evidence that with staging laparoscopy there is a risk of 10% of occult peritoneal disease in T3-4 tumors[2, 3]. In these patients the burden of surgery can be omitted if peritoneal disease is encountered and focus can shift towards palliative treatment strategies and possibly Hyperthermic Intraperitoneal Chemotherapy (HIPEC). In type II tumors there is no literature that supports the necessity of staging laparoscopy, but given the fact that the true cardia is intra-abdominal and that these tumors are often in an advanced stage at the time of diagnosis, also in type II an increased risk for intraperitoneal spread might exist which may be detected with staging laparoscopy. In the UMC Utrecht every operation in GEJ tumors starts with a laparoscopic examination combined with endoscopic evaluation of the extent of the cancer.

Considering the suboptimal accuracy of EUS and CT for location and tumor staging, other diagnostic modalities have been evaluated for their value in GEJ cancer. FDG-PET is becoming more prominent due to its improvements in diagnostic accuracy for detecting distant metastasis, however in the assessment of nodal status a recent meta-analysis demonstrated a poor sensitivity (51%) and specificity (84%)[4]. There are no studies reporting on the role of FDG-PET for determining tumor location. Also MRI is a topic of ongoing research, but the current evidence for detecting tumor location and lymph node status is still limited[5].

Neoadjuvant treatment

The type of neoadjuvant therapy for GEJ adenocarcinoma is a matter of debate. Several studies advocate the use of neoadjuvant chemoradiation[6, 7], while others prefer perioperative chemotherapy[8, 9]. However, none of the randomized controlled trials that have been published, distinguished between the various subtypes of GEJ tumors. Moreover, these studies primarily included patients with gastric or esophageal cancer with a subgroup of patients with tumors categorized as GEJ tumors. Therefore, with the current evidence it is not possible to decide which approach is more effective. In Chapter 3 it was demonstrated that perioperative chemotherapy was only beneficial in a small subgroup of patients (34%) who respond well to chemotherapy, whereas the majority (66%) had a poor response and consequently had worse outcome. This emphasizes the need for predictive biological or radiological tools to predict or assess chemotherapy sensitivity, but also stimulates the search for improved neoadjuvant treatment regimens. There is convincing evidence that preoperative chemoradiation effectuates an improved local control with more radical resections and higher pathological complete response and near-complete response rates[10], however a clear survival advantage of chemoradiation versus chemotherapy has not yet been reported. Furthermore, also with chemoradiation a large group of patients are poor responders and consequently have no benefit from the neoadjuvant treatment whereas this only adds up to overall morbidity[11]. Future research should therefore not only focus on the optimal neoadjuvant treatment regimen, but should also focus on prediction and assessment of neoadjuvant treatment sensitivity to alter the approach if necessary. This is important to incorporate an individualized treatment plan and to improve outcome in these patients.

Surgery

In Chapter 4 and 5 it was demonstrated that there is no clear evidence for the benefit of gastrectomy or esophagectomy in type II tumors regarding overall survival. However, there are several findings that should be addressed and warrant further research. First, patients treated with gastrectomy had more positive circumferential resection margins (CRM, 29%) compared to patient treated with esophagectomy (11%). In these patients, the positive CRM was always at the site of the esophagus. It seems that with gastrectomy it is more complicated to adequately dissect the distal esophagus, whereas the extensiveness and quality of the dissection improves with (transthoracic) esophagectomy. Furthermore, the extent of the proximal margin needed to optimize oncologic outcomes is unclear[12]. A large study reported an improved survival in case proximal margin length was greater than 3.8cm in >T2 tumors[13]. A disadvantage of the transabdominal approach is that the proximal margins are often limited due to obvious technical limitations of reaching the mediastinum from the hiatus.

Moreover, in Chapter 4 it was also demonstrated that patients with type II tumors will have upper mediastinal nodal involvement in 11% of the cases. In literature, studies consistently show that upper mediastinal nodal involvement will be present in 10-15% of the patients with type II tumors[14-16]. Although the most frequently involved lymph nodes are at the lesser curvature, which makes an intra-abdominal lymphadenectomy crucial. A transthoracic approach is the most reliable method of removing mediastinal lymph nodes. This was confirmed by a previous study that compared en-bloc transthoracic esophagectomy with a transhiatal approach in which the lymph node yield was significantly higher in the thoracotomy group[17]. Another study compared a transthoracic with transhiatal approach in T3N1 GEJ tumors and demonstrated an improved survival for the transthoracic group in case 8 or fewer lymph nodes involved[18]. Nevertheless, some surgeons advocate a transhiatal esophagectomy for type II tumors in case there is no evidence of mediastinal disease as this procedure is related with reduced morbidity. Indeed, in Chapter 3 it was demonstrated that the detection of lymph nodes was most reliable for upper mediastinal nodes with rates between 80 – 92%. Nonetheless, the accuracy is still not optimal and some patients with upper mediastinal nodal involvement could be missed. More importantly, it was also demonstrated that survival improved when an increasing number of lymph nodes were removed, even in node negative patients[19, 20]. Considering these findings all together, a reasonable approach for type II tumors would be a transthoracic esophagectomy to provide for improved local control and adequate lymph node dissection. However, level 1 evidence is lacking and future research, preferably a randomized controlled trial, is needed to confirm these findings and to provide more insight in the optimal approach.

In a selected group of patients with severe comorbidities and distal (type I) esophageal cancer, a transthoracic resection is deemed impossible causing too high risk of morbidity and mortality. In Chapter 6 it was demonstrated that in this patient group a transhiatal approach is a safe alternative offering a significant chance for cure. Indeed, still a substantial part of the patients develops major postoperative complications, which is associated with worse outcome. This reflects the importance to develop strategies to minimize postoperative morbidity. With the introduction of minimally invasive techniques, as demonstrated in Chapter 7, it is to be expected that morbidity rates will be reduced. However, this still needs to be proven in larger randomized controlled trials.

Postoperative course

Esophagectomy is complex surgery which is associated with substantial morbidity. Currently, there is considerable attention in the development of risk scores to preoperatively identify patients who are at risk for postoperative morbidity to select them for preoperative optimization to reduce complications. Other studies are focusing on new techniques that will aid in reducing complications rates, such as minimally invasive approaches and fast track recovery programs. In Chapter 8 we introduced the use of Intermittent Pneumatic Compression (IPC) as a new technique to reduce venous stasis during the long period of immobilization during surgery and during the immediate postoperative period in esophageal cancer surgery. It was demonstrated that IPC in addition to conventional thromboprophylaxis significantly reduced the incidence of symptomatic venous thromboembolic events (VTE) with 5.3%. This is an important finding that will aid in further reducing thrombo-embolic complication rates after esophagectomy.

Another postoperative complication is the occurrence of a hiatal hernia (HH). HH is becoming more noticed as long-term complication following esophagectomy due to improvements in survival. From a cohort study of 2 high-volume centers, the incidence was 7% as presented in Chapter 9. The most important finding is that a proportion of the patients will require emergency surgery. However, these patients will develop more postoperative complications and will have a prolonged Intensive Care Unit stay. Moreover, 2 patients died after emergency surgery. Therefore, the focus should lie on prevention of HH. A possible prevention method could be closure of the crurae during initial esophagectomy, which is advocated by some surgeons. However, there is no solid evidence supporting this and future studies will be required to validate this technique. Most patients will develop HH within 2 years after surgery as demonstrated in Chapter 9. Another possible way to improve outcomes is the use of routine screening after esophagectomy. This may lead to early recognition which could help select those patients that may benefit from elective surgery.

Survival

In the current TNM staging system only the number of lymph nodes is relevant for prognosis of the patient. However, previous studies described the importance of the location of metastatic lymph nodes and this could be confirmed by the study in Chapter 10[16, 21]. Patients with upper mediastinal nodal involvement (UM+) consequently had poor overall survival. Although we found that these patients had a higher N-stage compared to patients with UM+, multivariable analysis confirmed these findings. It seems UM+ in patients with GEJ adenocarcinoma represents a more advanced stage of the disease. This indicates the clinical importance of a new staging system that also incorporates the location of metastatic lymph nodes as a prognostic factor. To this extent, several authors proposed a revised classification system for esophageal and GEJ adenocarcinoma. Although these studies demonstrate a greater prognostic stratification than the current TNM edition, they yet need to be validated in large independent datasets[21, 22]. Furthermore, the study in Chapter 10 also demonstrated that neoadjuvant therapy has a significant impact on nodal status and distribution. The current TNM staging system is based on patients treated without neoadjuvant therapy. Since most patients currently are treated with a multimodal approach, efforts are on the way to update the TNM staging system to address the pathologic stage groupings after neoadjuvant therapy for esophageal and GEJ cancer[23].

In Chapter 11 it was demonstrated that patients with recurrent disease after esophagectomy for esophageal cancer have a poor prognosis of only 3 months. Especially patients with distant recurrence and more than 3 recurrent locations have worse post-recurrence survival. It is important to identify these patients because treatment with either chemotherapy or surgery might not be beneficial and only adds up to overall morbidity. To the contrary, in those patients with favorable prognostic factors (i.e. locoregional recurrence and ≤3 locations) treatment can prolong survival and may even lead to cure in selected patients. Future research can focus on this selected patient group to study the feasibility and potentially superior efficacy of new treatment approaches. Furthermore, in the Netherlands patients do not undergo routine diagnostic screening for recurrent disease after esophagectomy[24]. This could possibly lead to a more advanced disease at the time of diagnosis. Having in mind that most recurrences will develop in the first 2 years after surgery and patients with oligometastases have improved outcomes, routine screening in the first 2 years with either CT or PET-CT may lead to a larger patient group that is eligible for treatment with chemotherapy and/or surgery. This may ultimately lead to improved survival or even cure in these patients.

FUTURE PERSPECTIVES

This thesis has aimed to provide new insights in the field of management of gastroesophageal junction adenocarcinomas with a special focus on treatment strategy. As such, there are important considerations for further research. Regarding neoadjuvant therapy this thesis describes that perioperative chemotherapy is only beneficial in a small subgroup of patients. That noted, there is no solid evidence in literature that proves the superiority of chemoradiation in GEJ adenocarcinoma. Further research that compares neoadjuvant chemoradiation versus chemotherapy is needed to provide more insight in the optimal neoadjuvant approach. Importantly, it would also be valuable to assess biomarker expression in preoperatively collected biopsy material, which in combination with clinical data might enable to predict response to neoadjuvant therapy. This could ultimately lead to individualized treatment protocols. To this extent, we have set up a nationwide database with eight UMCs as part of the Parelsnoer Institute to collect clinical information and biomaterial of patients with esophageal and gastric cancer (Esophageal and Gastric Cancer Pearl)[25]. This will provide opportunity for future studies to gain more insight in the etiology, treatment and prognosis of esophageal and gastric cancer.

Due to improved local control with esophagectomy and the given potential sites of nodal disease in type II tumors as presented in this thesis, it might be reasonable to approach type II tumors as esophageal cancer by means of a transthoracic esophagectomy. However, our data could not demonstrate a long-term survival benefit of esophagectomy. In literature, there is not enough empiric data regarding type II tumors and their clinical behavior to determine how to best manage them. Therefore, future research should focus on the optimal surgical approach in these tumors. It would be of interest to design a randomized controlled trial that compares esophagectomy versus gastrectomy. An obstacle that needs to be encountered, however, is the difficulty to preoperatively determine the exact tumor location as presented in this thesis. A considerable number of patients would not be included because they would preoperatively be classified as a type I tumor. To overcome this problem, randomization could be performed intraoperatively after determining the exact tumor location. A second trial which would be also be very interesting to perform, is the comparison of a transthoracic versus a transhiatal approach in GEJ adenocarcinoma. This trial is currently being set up and will be the first trial to compare transthoracic with transhiatal esophagectomy in the current era of multimodality treatment and minimally invasive surgery. Hopefully, this trial will bring more insight in the optimal surgical approach for GEJ adenocarcinoma.

CONCLUSIONS

Part I: staging and treatment

1. The accuracy of EUS and CT is suboptimal for determining tumor location and lymph node status in GEJ adenocarcinomas, nevertheless only a small number of patients needed a change of strategy during surgery.
2. EUS is superior to CT in determining tumor and lymph node location in GEJ adenocarcinoma.
3. Neoadjuvant chemotherapy in GEJ adenocarcinomas is only beneficial in one third of the patients who respond well to chemotherapy.
4. An esophagectomy might be preferable in type II tumors due to improved local control and appropriate lymphadenectomy of the upper mediastinal nodes.
5. The administration of neoadjuvant therapy has more impact on overall survival than surgical approach in GEJ adenocarcinomas.

6. Transhiatal esophagectomy is a safe alternative in patients with an elevated risk for surgery, offering a significant chance for cure.
7. A minimally invasive approach in transhiatal esophagectomy is safe and feasible, with evidence of reduced blood loss a shorter hospital stays.

Part II: postoperative course and survival

8. Intermittent pneumatic compression in addition to standard thromboprophylaxis reduces the incidence of venous thromboembolic events in patients treated with esophageal cancer surgery.
9. Hiatal hernia is a significant long-term complication after esophagectomy and emergency surgery should be avoided at all costs due to dismal outcomes.
10. Location of metastatic lymph nodes in patients with an adenocarcinoma of the GEJ is predictive of overall survival.
11. In patients with recurrent disease after esophagectomy for cancer, distant recurrence and more than 3 recurrent locations are associated with worse post-recurrence survival, irrespective of primary tumor characteristics.

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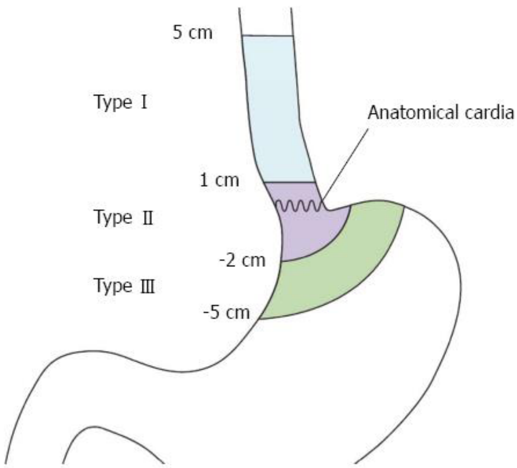
Chapter 14

Nederlandse samenvatting

SAMENVATTING

Slokdarmkanker is een agressieve vorm van kanker, waarvan de incidentie nog altijd toeneemt. Dit komt met name door de stijgende incidentie van het adenocarcinoom van de gastro-oesofageale overgang of junctie (GEJ). Dit is een tumor die precies op de overgang tussen de slokdarm en maag zit. Deze tumoren kan je indelen in 3 types volgens het classificatiesysteem van Siewert (zie figuur onder). Type I is een tumor die zit van 5cm tot 1cm boven de anatomische overgang van slokdarm naar maag en wordt distaal oesofaguscarcinoom of tumor van het laatste deel van de slokdarm genoemd. Type II zit op 1cm boven en 2cm onder de anatomische overgang en wordt gezien als het ware cardiacarcinoom of overgangstumor. Type III zit van 2cm tot 5cm onder de anatomische overgang en wordt gezien als een subcardiaal maagcarcinoom of tumor van het bovenste gedeelte van de maag.



Figuur 1 Siewert classificatie

Per jaar worden in Nederland ongeveer 500 patiënten met deze ziekte gediagnosticeerd. Over de optimale behandelingsstrategie voor deze tumoren bestaat nog veel onduidelijkheid. Chirurgie is de belangrijkste pijler in het bereiken van genezing, echter de laatste jaren is er steeds meer bewijs voor het gebruik van neoadjuvante therapie d.w.z. behandeling met chemo(radio)therapie voor de operatie. Echter, doordat GEJ tumoren precies op de overgang van slokdarm naar maag zitten, bestaat er discussie over de juiste vorm van neoadjuvante therapie als ook de soort chirurgie. Een veel gebruikte vorm van chirurgie is de slokdarmresectie. Dit is een ingrijpende operatie, waarbij de slokdarm in zijn geheel wordt verwijderd en er een nieuwe buis wordt gemaakt van de maag. Er worden steeds betere chirurgische technieken toegepast en de zorg tijdens en na de operatie wordt steeds verder geoptimaliseerd, echter deze operatie blijft erg ingrijpend en gaat gepaard met veel complicaties. De 5-jaarsoverleving van patiënten met deze ziekte is de afgelopen jaren toegenomen door het toenemende gebruik van neoadjuvante therapie en door verbetering van de chirurgie en de zorg rondom de operatie. Desondanks is de prognose slecht doordat veel mensen een recidief (terugkeer van de ziekte) krijgen. Het doel van het onderzoek in dit proefschrift is om de huidige behandelingsstrategieën voor het adenocarcinoom van de gastro-oesofageale overgang te evalueren en te onderzoeken wat de optimale benadering is voor de echte overgangstumoren. Daarnaast worden een aantal belangrijke complicaties na de operatie in kaart gebracht. Als laatste wordt gekeken naar prognostische factoren die van invloed zijn op de overleving.

DEEL 1: PREOPERATIEVE SCREENING EN BEHANDELING

Preoperatieve screening van het adenocarcinoom van de GEJ is noodzakelijk om de behandelingsstrategie in de vorm van neoadjuvante therapie en chirurgie te bepalen. Daartoe zijn er verschillende diagnostische technieken in gebruik. Onder andere wordt standaard een kijkonderzoek van slokdarm en maag verricht in combinatie met inwendige echografie (EUS). Daarnaast wordt standaard een CT scan gemaakt van de borstkas en buik. In **Hoofdstuk 2** wordt bekeken hoe accuraat deze diagnostische technieken zijn in het bepalen van de exacte tumorlocatie en in het bepalen van uitzaaiingen in lymfklieren. Dit hebben we onderzocht in groep van 266 patiënten met een adenocarcinoom van de GEJ in het UMC Utrecht. De algehele nauwkeurigheid voor het bepalen van de tumorlocatie was 73% voor EUS en 61% voor CT. De nauwkeurigheid voor het bepalen of een bepaalde lymfklier uitzaaiingen bevatte was 77% voor EUS en 71% voor CT. De nauwkeurigheid was met name goed voor klieren die zich hoog in de borstkas (hoog mediastinaal) bevonden (waarden tussen 80 – 92%) terwijl deze verslechterde voor klieren die zich rondom de tumor en in de bovenbuik bevonden (waarden tussen 50 – 82%). Alhoewel de nauwkeurigheid

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voor het bepalen van de tumorlocatie suboptimaal was, was er maar in 3% van de patiënten een strategiewijziging tijdens de operatie noodzakelijk. Daarnaast kon in 88% van de patiënten de tumor volledig worden verwijderd. Dit onderzoek laat zien dat EUS beter is dan CT in het bepalen van tumorlocatie en locatie van lymfklieruitzaaiingen en dat deze modaliteit een belangrijke rol speelt bij het bepalen van de juiste behandelingsstrategie.

De optimale neoadjuvante therapie voor GEJ adenocarcinomen is nog onduidelijk. Het doel van het onderzoek in **Hoofdstuk 3** was om te bepalen wat de toegevoegde waarde is van neoadjuvante chemotherapie voor de operatie in 196 patiënten met een adenocarcinoom van de GEJ. Van deze 196 patiënten zijn 124 voorbehandeld met chemotherapie en heeft de rest de operatie gehad zonder voorbehandeling. Tussen beiden groepen kon geen verschil worden aangetoond in ziektevrije overleving en totale overleving. In 32 van de voorbehandelde patiënten (34%) was er een goede respons gezien op chemotherapie, d.w.z. de tumor was aanzienlijk geslonken. In deze patiënten was de 5-jaarsoverleving 67%, welke een stuk beter was dan de 35% in patiënten die niet zijn voorbehandeld. Echter, het grote deel van de voorbehandelde patiënten (66%) heeft een slechte respons op chemotherapie, d.w.z. de tumor was niet geslonken of zelfs groter geworden. Juist in deze patiënten werden tijdens de follow-up meer recidieven gevonden en was de 5-jaarsoverleving slechts 21%. Dit betekent dat voorbehandeling met chemotherapie alleen van toegevoegde waarde is in een klein deel van de patiënten die hier sensitief voor zijn. Daarom is het belangrijk om voorspellende biologische en radiologische factoren te vinden die de sensitiviteit van chemotherapie voor de start van behandeling kan voorspellen of tijdens de behandeling kan vaststellen om zo de eventuele behandelingsstrategie te kunnen aanpassen indien noodzakelijk.

Het adenocarcinoom van de GEJ bestaat uit 3 types. De chirurgische behandeling van type I bestaat over het algemeen uit een slokdarmresectie, waarbij de slokdarm in zijn geheel wordt verwijderd en een nieuwe verbinding wordt gemaakt met de maag. Voor type III is de meest gebruikte chirurgische behandeling een totale maagresectie, waarbij de maag in zijn geheel wordt verwijderd en een nieuwe verbinding tussen de slokdarm en dunne darm wordt gemaakt. Over de optimale chirurgische behandeling van type II tumoren, de echte overgangstumoren, bestaat nog veel discussie. In **Hoofdstuk 4** onderzoeken we de weefselkarakteristieken en het klinische beloop na een slokdarm- en maagresectie in 176 patiënten met een type II tumor. In totaal heef

86% een slokdarmresectie gehad en 14% een maagresectie. De algehele overleving in beide groepen was vergelijkbaar en er werden geen verschillen gevonden met betrekking tot mortaliteit, complicaties na de operatie en het ontwikkelen van een recidief. Wel zagen we dat bij een maagresectie de tumor in 71% van de patiënten in zijn geheel verwijderd was (radicale resectie), ten opzichte van 89% bij patiënten met een slokdarmresectie. Tevens zien we dat 11% van de patiënten uitzaaiingen heeft in hoog mediastinale lymfklieren, welke alleen meegenomen kunnen worden met een slokdarmresectie. Op basis van deze bevindingen lijkt een slokdarmresectie voor type II tumoren de voorkeur te hebben.

Het doel van het onderzoek in **Hoofdstuk 5** was om de verschillende behandelingsstrategieën van het GEJ adenocarcinoom te evalueren in een landelijke database. Totaal zijn 939 patiënten geïncludeerd die een slokdarmresectie hebben ondergaan en 257 patiënten met een maagresectie. Tussen beiden groepen zijn geen verschillen gevonden in het aantal meegenomen lymfklieren en radicaliteit van de resectie. De 5-jaarsoverleving was 36% na slokdarmresectie en 33% na maagresectie, dit verschil was niet significant. In een multivariabele analyse werd geen verschil gevonden tussen slokdarm- en maagresectie met betrekking tot overleving. Wel hadden patiënten die zijn voorbehandeld met neoadjuvante therapie een betere overleving dan patiënten die niet zijn voorbehandeld. Derhalve kunnen we van deze studie concluderen dat neoadjuvante therapie een belangrijkere factor is in overleving dan soort chirurgie in patiënten met een GEJ adenocarcinoom.

Patiënten met slokdarmkanker en ernstige comorbiditeiten, d.w.z. ernstige bijkomende ziekten zoals hart- en vaatziekten, longziekten etc., komen doorgaans niet in aanmerking voor een transthoracale slokdarmresectie. Dit is een ingrijpende operatie waarbij de slokdarm wordt verwijderd via een operatie in de borstkas en een operatie in de buik. Bij een transhiatale slokdarmresectie (THE) wordt de slokdarm alleen verwijderd via een operatie in de buik. Dit gaat gepaard met minder complicaties, echter kunnen hierdoor niet alle lymfklieren in de borstkas worden meegenomen. Het doel van het onderzoek in **Hoofdstuk 6** is om het klinische beloop na de operatie en algemene overleving te evalueren in 68 patiënten met slokdarmkanker die ernstige comorbiditeiten hebben en daarom zijn behandeld met THE. Een postoperatieve complicatie kwam voor in 66% van de patiënten. De meeste ontwikkelden een lekkage van de nieuw aangesloten verbinding (35%), longontsteking (34%) of hartritmestoornis (22%). Ondanks dat in 35% van de patiënten de complicatie ernstig was waardoor patiënten opnieuw geopereerd moest worden of behandeling op de Intensive Care moesten ondergaan, was de mortaliteit na de operatie maar 3% en was na 5 jaar 36% nog in leven. De lage mortaliteit en goede 5-jaarsoverleving laat zien dat ingrijpende chirurgie zoals THE in deze patiëntengroep met ernstige comorbiditeiten zeker de moeite waard is en een goede kans op overleving kan bieden.

Door het opereren via laparoscopie (kijkoperatie), een nieuwe techniek waarbij kleine sneden worden gemaakt voor de instrumenten in plaats van de standaard open operatie waarbij een grote snede wordt gemaakt, kunnen complicaties na de operatie worden verminderd. Dit is tot nu toe echter alleen onderzocht in transthoracale slokdarmresecties. In **Hoofdstuk 7** wordt een systematische review van de literatuur gedaan om de huidige status en toegevoegde waarde van laparoscopie bij THE te evalueren. In totaal werden 4 studies geïncludeerd die laparoscopie vergelijken met open THE. In alle studies werd minder bloedverlies en kortere ziekenhuisduur gezien bij laparoscopie. Er werden geen verschillen gevonden in operatietijd, postoperatieve complicaties, radicaliteit en aantal lymfklieren. Op basis van deze eerste 'pilot' studies blijkt laparoscopie bij THE veilig en uitvoerbaar te zijn, waarbij er aanwijzingen zijn voor minder bloedverlies en kortere ziekenhuisduur. Echter, het bewijs is nog niet voldoende en verder onderzoek is noodzakelijk om de bevindingen te bevestigen alsook om te kijken naar lange-termijn uitkomsten.

DEEL II: POSTOPERATIEF BELOOP EN OVERLEVING

Veneuze trombose, waaronder trombosebeen en longembolie, zijn bloedstolsels in het bloed die ernstige complicaties kunnen geven. De kans op veneuze trombose is verhoogd bij patiënten met kanker en patiënten die lang stilliggen tijdens een ingrijpende operatie. Derhalve is het een veelvoorkomende complicatie na een slokdarmresectie voor kanker. Een nieuwe techniek die is ontwikkeld om veneuze trombose tegen te gaan is intermitterende pneumatische compressie (IPC), ofwel een mechanische pomp die tijdens de operatie aan beide benen wordt aangesloten om ervoor te zorgen dat het bloed in beweging blijft en niet de kans krijgt om stolsels te vormen. Echter, het gebruik van deze techniek is nog niet eerder onderzocht bij slokdarmresecties. Derhalve is het onderzoek in **Hoofdstuk 8** opgezet waarbij wordt gekeken naar veneuze trombose na slokdarmresectie in 195 patiënten die IPC hebben gehad en in 118 patiënten zonder IPC. In de groep patiënten die IPC heeft gehad ontwikkelde 1.5% na de operatie veneuze trombose in vergelijking met 6.8% van de patiënten die geen IPC heeft gehad. Daaruit blijkt dat IPC een effectieve maatregel is om veneuze trombose na de operatie te verminderen bij patiënten die een slokdarmresectie ondergaan.

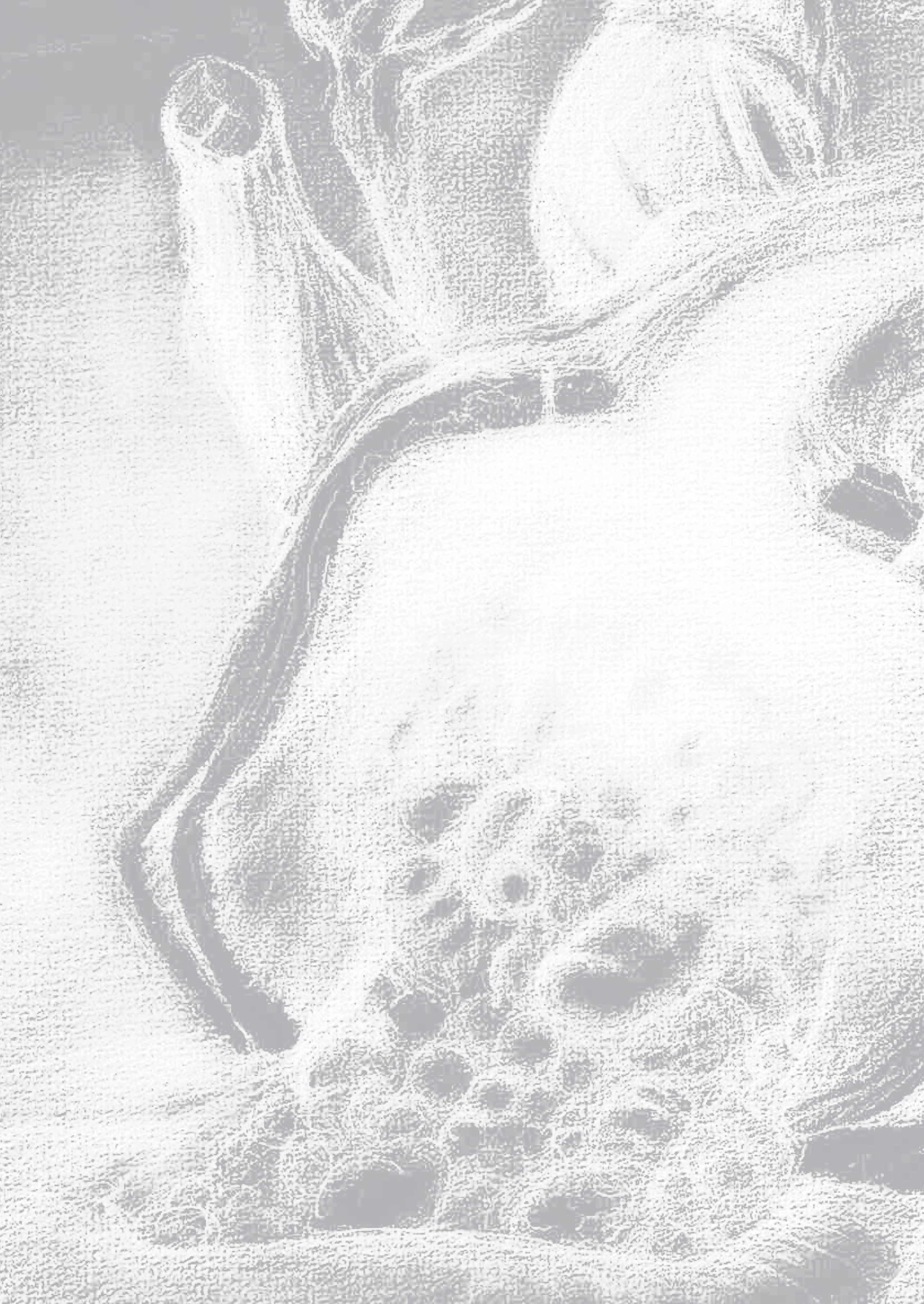
Bij een hiatus hernia (HH) of middenrif breuk komen organen die normaliter in de buik horen te liggen, door het middenrif in de borstkas te liggen. Dit is een lange-termijn complicatie die kan voorkomen na een slokdarmresectie en kan ernstige gevolgen geven indien bijvoorbeeld de dikke- of dunne darm in de borstkast wordt afgekneld. Er zijn onderzoeken die suggereren dat HH vaker voorkomt na de introductie van laparoscopie. Het onderzoek in **Hoofdstuk 9** was uitgevoerd om te kijken hoe vaak HH na slokdarmresectie voorkomt, wat het klinische beloop is en of laparoscopie de kans op HH verhoogd. In totaal zijn 657 patiënten geëvalueerd, waarbij uiteindelijk 44 patiënten (7%) een HH ontwikkelden. Er was geen verschil gevonden tussen laparoscopische en open chirurgie. Een spoedoperatie, omdat zich een levensbedreigende situatie voordeed, was nodig in 16 patiënten. Deze patiënten lagen gemiddeld langer op de Intensive Care dan de 10 patiënten waarbij een operatie electief werd ingepland. Bij de overige patiënten met HH werd een conservatief beleid gevoerd. Op basis van deze studie kunnen we concluderen dat HH een belangrijke lange-termijn complicatie is na slokdarmresectie, waarbij de incidentie niet wordt verhoogd door laparoscopie. Een spoedoperatie moet zoveel mogelijk worden voorkomen.

De aanwezigheid van uitzaaiingen in lymfklieren wordt gezien als een prognostisch ongunstige factor voor overleving in patiënten met GEJ adenocarcinoom. Echter, het is niet duidelijk of de locatie van waar de lymfklieruitzaaiingen zich bevinden ook van invloed is op de overleving. De meest voorkomende lymfklierstations waar uitzaaiingen kunnen ontstaan, zijn rondom de maag, middenrif en het laatste deel van de slokdarm. Echter uitzaaiingen kunnen ook hoog rond de slokdarm zitten (hoog mediastinaal). In **Hoofdstuk 10** onderzoeken we in 199 patiënten met een adenocarcinoom van de GEJ in hoeverre de locatie van lymfklieruitzaaiingen belangrijk is voor de algehele overleving. Van alle patiënten hadden 116 (58%) lymfklieruitzaaiingen. Uitzaaiingen in hoog mediastinale klieren werd gezien in 27 patiënten (14.1%), terwijl 80 patiënten wel lymfklieruitzaaiingen hadden, maar niet hoog mediastinaal. Patiënten met hoog mediastinale lymfklieruitzaaiingen ontwikkelden meer recidieven en hadden daardoor een slechte 5-jaarsoverleving van 14% terwijl in patiënten met lymfklieruitzaaiingen zonder hoog mediastinale klieren een 5-jaarsoverleving van 29% werd gezien. Dit laat zien dat de locatie van lymfklieruitzaaiingen wel degelijk van invloed is op de algehele overleving en daarom is het belangrijk om deze factor mee te nemen in toekomstige classificatiesystemen.

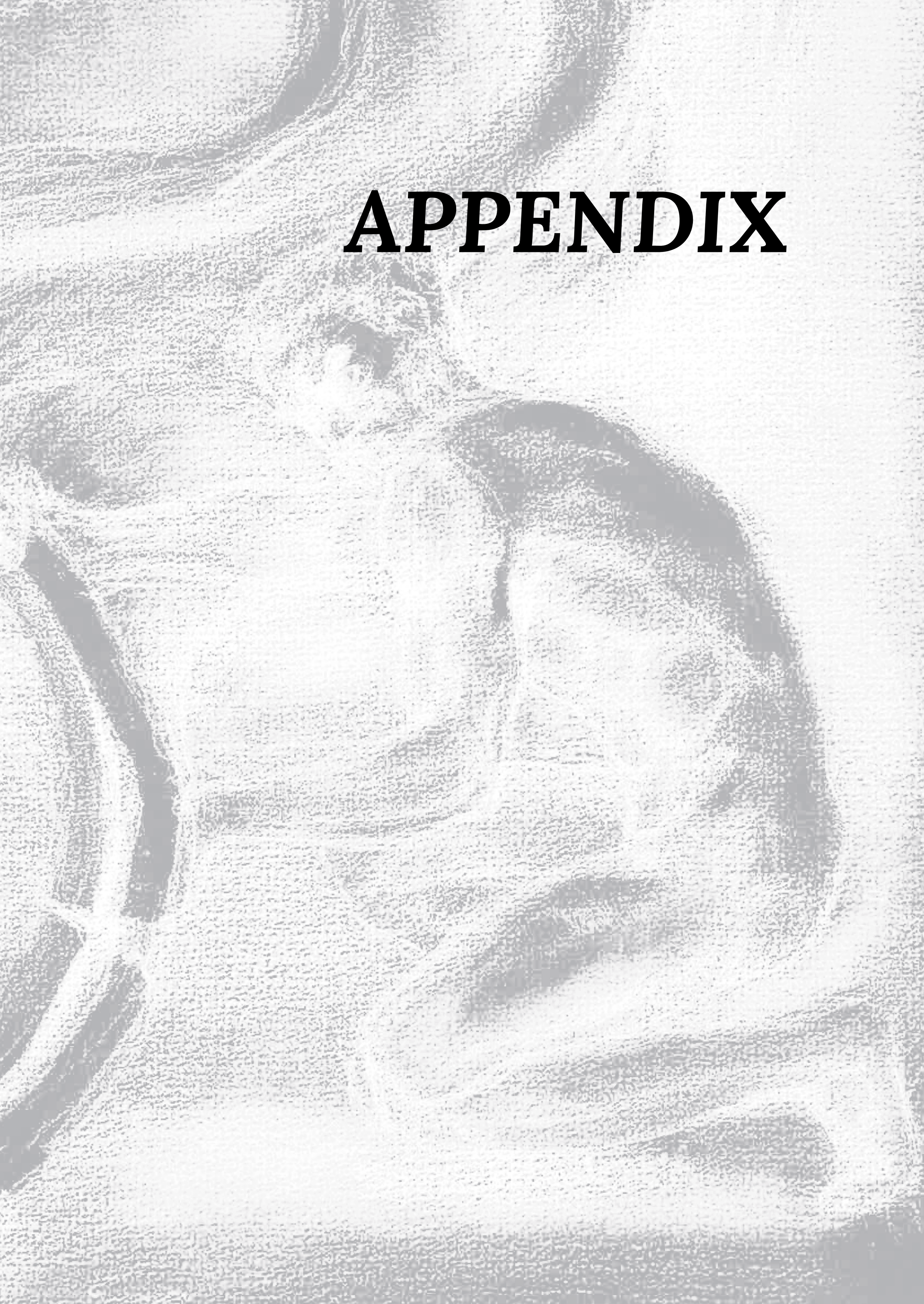
Het doel van het onderzoek in **Hoofdstuk 11** was om prognostische factoren te identificeren die van invloed zijn op de algehele overleving in de groep van patiënten die een recidief heeft ontwikkeld na eerdere slokdarmresectie voor kanker. Uitzaaiingen op afstand (in tegenstelling tot lokaal in het operatiegebied) en uitzaaiingen op meer dan 3 verschillende locaties zijn factoren die gepaard gaan met een zeer ongunstige overleving. Gemiddeld hebben patiënten die een recidief ontwikkelen nog maar 3 maanden te leven, wat de agressiviteit van deze ziekte weergeeft. Desondanks kan in een selecte groep patiënten behandeling in de vorm van chemotherapie of zelfs chirurgie lijden tot betere overleving en mogelijk zelfs genezing. Dit weerspiegelt het belang van zorgvuldige evaluatie van patiënt en tumorkarakteristieken om te bepalen of een behandeling de moeite waard is in de individuele patiënt.

CONCLUSIE

In het eerste deel van dit proefschrift laten we zien dat voorbehandeling met chemotherapie voor deze tumoren alleen van toegevoegde waarde is in een derde van de patiënten die hiervoor sensitief zijn. Daarom is het belangrijk om voorspellende biologische en radiologische factoren te vinden die de sensitiviteit van chemotherapie voor de start van behandeling kan voorspellen of tijdens de behandeling kan vaststellen om zo de eventuele behandelingsstrategie te kunnen aanpassen indien noodzakelijk. Met betrekking tot chirurgie (bij type II tumoren) zagen we dat bij een maagresectie de tumor in 71% van de patiënten in zijn geheel verwijderd was, ten opzichte van 89% bij patiënten met een slokdarmresectie. Tevens zien we dat 11% van de patiënten uitzaaiingen heeft in hoog mediastinale lymfklieren, welke alleen meegenomen kunnen worden met een slokdarmresectie. Echter, multivariable analyse liet geen significant verschil zien op overlevingsduur tussen beiden chirurgische technieken. Dit werd bevestigd in de landelijke database, waaruit blijkt dat neoadjuvante therapie een grotere invloed heeft op overleving. Verder onderzoek is nodig om de optimale behandelstrategie voor type II tumoren te bepalen. In het tweede deel van het proefschrift laten we zien dat het gebruik van IPC ter preventie van veneuze trombose na slokdarmresectie een effectieve maatregel is om veneuze trombose in deze patiënten te verminderen. Daarnaast zijn locatie van positieve lymfklieren en locatie en aantal recidieven belangrijke voorspellers van algehele overleving.



APPENDIX



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ACKNOWLEDGMENTS (DANKWOORD)

Bij deze alvast IEDEREEN bedankt, dan ben ik in ieder geval niemand vergeten. De afgelopen drie jaar hebben in het teken gestaan van dit proefschrift. Ik had dit absoluut niet zonder de bijdrage, inspanning en steun van vele anderen kunnen doen. Een aantal van hen wil ik in het bijzonder bedanken.

Beste Prof. Dr. R van Hillegersberg, beste Richard, ik klopte bij je aan als student en vanaf het eerste moment voelde ik steun en vertrouwen. Ik ben je ontzettend dankbaar voor alle wijze lessen van de afgelopen jaren en ik waardeer de kritische blik en diepgang die in het onderzoek wordt gestoken enorm. Onder jouw vleugels is de onderzoeksgroep uitgegroeid tot een fantastische groep die onderzoek bedrijft op het hoogste niveau. Ik ben dan ook trots om hiervan deel uit te maken.

Beste Dr. Ruurda, beste Jelle, wat was het fijn om een copromotor te hebben die zo efficiënt werkt als jij. Mails die in korte tijd worden beantwoord en manuscripten die meestal binnen een paar dagen weer gereviseerd terugkwamen, hebben ervoor gezorgd dat ik direct weer verder kon. Daarnaast ben je enthousiast, to the point en niet schuw van een paar goede grappen. Kortom, ik heb een enorm leuke en leerzame tijd met jou gehad en daar wil ik je hartelijk voor bedanken.

De leden van de beoordelingscommissie, Prof. Dr. M.G.E.H. Lam, Prof. Dr. G.J.A. Offerhaus, Prof. Dr. P.O. Witteveen, Prof. Dr. E. van der Wall en Prof. Dr. D.L. van der Peet, hartelijk dank voor uw tijd en interesse in mijn proefschrift en de bereidheid zitting te nemen in de oppositie.

En dan de onderzoeksgroep, ik had geen betere kunnen wensen. Onder andere de productieve researchmeetings, de enorm goede sfeer op congressen, de slechte grappen via de app, de eeuwige voetbalrivaliteit en de ingeplande borrels met morning after pics van jut en jul hebben mijn onderzoekstijd fantastisch gemaakt. Leonie Haverkamp, dank voor je begeleiding tijdens mijn studententijd, daar zijn 2 topartikelen uit gekomen. Peter van Rossum, je kritische blik en hulp bij statistiek heb ik zeer gewaardeerd. Lucas Goense, vaak hebben we onder het genot van een koffie het onderzoeksleven besproken, waarbij je soms heerlijk 'jezelf' kunt zijn, heel chill. Hylke Brenkman en Maarten Seesing, the fun and joy van onze groep. Ik geniet dagelijks van jullie enthousiasme en de fijne grappen en foto's via de app. Els Visser, ik

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ben blij dat ik jou heb kunnen inwijden in de wereld van de Parel. Teus Weijs, Margriet Prins, Pieter van der Sluis, Alicia Borggreve en Sylvia van der Horst, allen zeer dank voor jullie bijdrage aan de mooie tijd die ik heb gehad.

Beste Romy, Mariëlle en Fatiha, jullie zijn een zeer belangrijke schakel in het traject van vele onderzoekers. Ondanks de drukke agenda's van de chirurgen weten jullie altijd tot oplossingen te komen. Daarnaast hebben jullie mij op veel andere vlakken geholpen, waarvoor veel dank!

De Toren, mijn thuishaven. Jakob Kist, Laurien Waaijer, Stefanie Peters-Weem, Sjoerd Nell, Tesse Leunissen en Steven van Haelst. Jullie hebben ervoor gezorgd dat ik mij iedere dag thuis voelde. Niet alleen werd er zo nu en dan 'serieus' gewerkt, veelvuldig stond de sfeer in het teken van lachen. Ik heb genoten van de nespresso's, de dumpert filmpjes, het geroddel en alle mooie borrels en feestjes die we de afgelopen jaren hebben gehad. Dank voor de geweldige tijd guys!

Alle promovendi, stafleden en assistenten van de chirurgie in het UMC Utrecht. Chirurgie is het mooiste vak dat er is en jullie als groep laten dat elke dag zien. Ik heb me altijd thuis gevoeld. Veel dank voor de geweldige tijd die ik heb gehad op symposia, borrels en natuurlijk de skireis. In het bijzonder gaat mijn dank uit naar: Lutske Lodewijk, Kari Trumpi, Jennifer Jongen, Pieter Leliefeld, Morsal Samim, Marieke Walma, Mark Haverkort, Thomas Vellinga, Amy Gunning, Maarten Burbach, Djurre de Waard, Steffi Rombouts en Vanessa Pourier.

Dank aan alle collega's van de chirurgie in het Meander. Ik heb het afgelopen jaar een bijzonder leerzame en leuke tijd gehad. Het is een hechte groep en ik geniet met name van de fijne sfeer die er hangt. Het was ontzettend fijn om bij jullie te werken!

Thanks to all the guys in Southampton, especially: Tim Underwood, Annette Hayden and Fergus Noble. I learned much from you guys in the lab. You were very welcoming and because of you my stay in England was very pleasant.

En dan is er natuurlijk speciale ruimte voor de belangrijkste mensen in mijn leven: familie en vrienden!

Allereerst mijn paranimfen, dank dat jullie aan mijn zijde staan. Daan 'Swinky' Winters, de eeuwige sfeermaker. Wat ben ik blij dat ik jou in Groningen heb leren kennen. Je bent een geniale vent en ik ben blij als ik met je kan lachen op borrels, weekendjes weg, fietsvakanties en nog veel meer. Lieve Gé-Ann, jij was en bent mijn 'geneeskunde' maatje. Samen hebben we heel wat uurtjes in de CMB doorgebracht. Met jou ben ik begonnen aan de wijde wereld van de wetenschap met als slagroom op de taart ons waanzinnig congres in Rome. Ik hoop dat we nog veel meer hoogtepunten gaan beleven!

The boys van Gouda: Jorna, Rem en Jamall. Als sinds ons 12de beste maten en daar zal geen verandering meer in komen. Ik mag mijzelf gelukkig prijzen dat ik omringt ben door zulke goede vrienden. We hebben al zoveel mooie dingen samen beleefd en ik weet zeker dat er nog zoveel fantastische dingen gaan komen. Thanks for having my back!

Ubbens en Kleef, lichting! En natuurlijk de rest van het GHD. Er bestaat geen leven zonder ontspanning en met jullie is het altijd feest. Hetzelfde geldt voor de mannen van Hertog.

Mickey, kleine broertje van me. Naarmate je ouder wordt, merk ik steeds meer hoeveel wij gemeen hebben. Zet ons in een kamer en het is alleen maar lachen, gieren en brullen. Ik merk dat onze band alleen maar beter wordt en daar ben ik erg blij mee. Lindsey, lieftallige zus. Dank dat ik bij jou en Steven altijd welkom ben. Jouw gezin, met Jayson and Brody, is mij ontzettend dierbaar.

Lieve mam en dad, we zijn een familie van weinig woorden, maar sommige dingen mogen gezegd worden. Ik ben blij met de onvoorwaardelijke steun die ik van jullie krijg, die hebben geleid tot waar ik nu ben. Ik prijs mij gelukkig met jullie als ouders. Dank voor alles, en nog veel meer.

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1. Intermittent pneumatic compression in combination with low-molecular weight heparin in the prevention of venous thromboembolic events in esophageal cancer surgery. **Parry K**, Sadeghi AH, van der Horst S, Westerink J, Ruurda JP, van Hillegersberg R. J *Surg Oncol*, 2016 *[in press]*

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14. Influence of the location of positive lymph nodes on survival in patients with gastroesophageal junction tumors. Parry K, Ruurda JP, Brosens LA, Cuesta MA, van Hillegersberg R. *Submitted for publication*

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CURRICULUM VITAE

Kevin Parry was born on the 7th of August 1988 in Alkmaar, the Netherlands. In 2006 he graduated from secondary school, the Coornhert Gymnasium in Gouda. Hereafter, he moved to Groningen to start his medical school at the University of Groningen. During his study, he performed research at the Department of Pediatric Surgery, which has led to his first presentation at an international conference in Rome in 2012. Also, he worked for 2 years as a student-assistant for the Liver Transplant Team, providing assistance during liver transplantations. In his last year of medical school, he moved to Utrecht to perform his final internship and research project at the department of Surgical Oncology of the UMC Utrecht.

After graduating in 2014, he commenced a PhD program at the department of Surgery in the UMC Utrecht focusing on staging and treatment of adenocarcinomas of the GEJ under supervision of Prof. Dr. R. van Hillegersberg and Dr. J.P. Ruurda. The results of his research are presented in this thesis and were published in several international peer-reviewed scientific journals. During his PhD he also helped set up the Esophageal and Gastric Cancer Pearl, a national clinical biobanking project in the Netherlands. In 2016 he started his clinical career as a medical doctor at the Meander Medical Center in Amersfoort as ANIOS of general surgery.

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