

# **Reducing Pulmonary Complications After Esophagectomy For Cancer**

Maarten Frans Johan Seesing

## **Reducing Pulmonary Complications After Esophagectomy For Cancer**

PhD thesis, Utrecht University, The Netherlands

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# Reducing Pulmonary Complications After Esophagectomy For Cancer

Bestrijding van pulmonale complicaties  
na slokdarmresectie voor kanker  
(met een samenvatting in het Nederlands)

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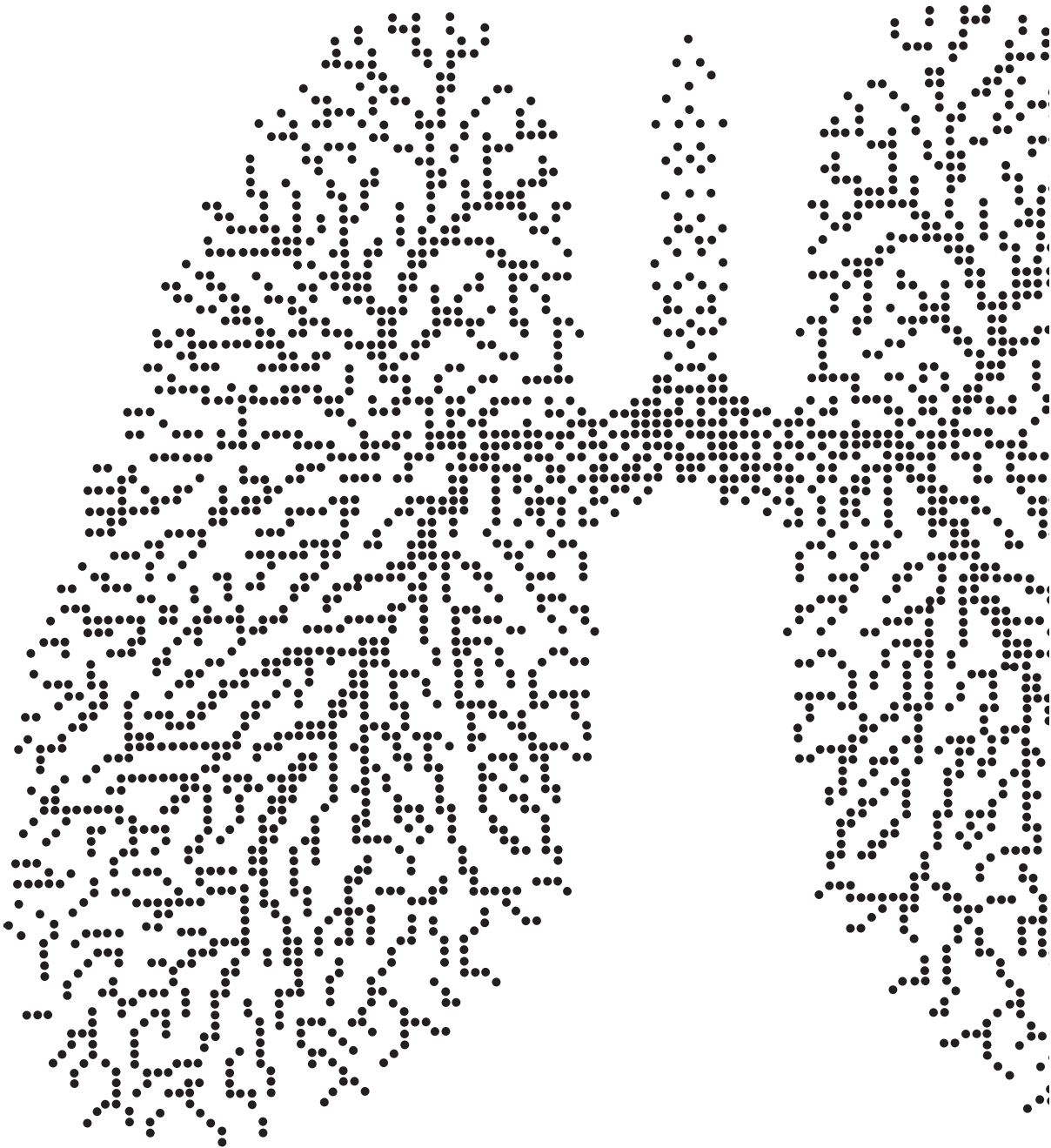
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# Chapter 1

General introduction  
and thesis outline

# General introduction

## Esophageal Cancer

Esophageal cancer has a fast-growing incidence. It is the eight most common cancer worldwide, with 456.000 patients diagnosed annually. Moreover, it is an aggressive disease, illustrated by the annual worldwide cancer-related mortality rate of approximately 406.800.<sup>1</sup> The presenting signs and symptoms of gastroesophageal junction or esophageal cancer tend to reflect the local extent of the tumor and do typically occur late in its course.<sup>2</sup> This is highlighted by the fact that at the time of diagnosis, only 1 in every 4 patients with gastroesophageal junction or esophageal cancer is eligible for treatment with curative intent.<sup>3,4</sup> Weight loss and dysphagia in a patient with a history of alcohol and tobacco use used to be the classical presentation of a patient with a squamous cell carcinoma of the esophagus.<sup>2</sup> However, with a rising incidence of adenocarcinoma of the distal esophagus, partially due to an increasing incidence of obesity in western society, complaints of gastroesophageal reflux are becoming more dominant.<sup>5</sup>

The cornerstone of curative care for esophageal cancer is neoadjuvant chemoradiotherapy followed by esophagectomy with a two-field lymphadenectomy.<sup>6</sup> Following multimodality treatment with curative intent, the median disease free survival is approximately 37 months and the median overall survival is 48 months.<sup>7</sup> Although many advances in surgical techniques have already been made, postoperative morbidity remains high, with morbidity and mortality incidences reported up to 65% and 15% respectively.<sup>8</sup>

## Minimally Invasive Surgery

Minimally invasive surgery has become the standard of care in many surgical procedures. The use of minimally invasive techniques may reduce blood loss, postoperative pain and complications. This generally leads to a shorter hospital stay and an improved quality of life. Nevertheless, the standard surgical approach for esophagectomy has always been by means of a laparotomy or a combined laparotomy and thoracotomy.<sup>9,10</sup> The first thoracoscopic esophagectomy was performed in 1992 by Sir Alfred Cuschieri, a pioneer in minimally invasive surgery.<sup>11</sup> A trend towards minimally invasive surgery in esophageal cancer care is ongoing, however its definitive value remains to be demonstrated.

The only randomized controlled trial comparing open and minimally invasive esophagectomy published to date (TIME trial) demonstrated a shorter hospital stay, a reduction of postoperative pulmonary infections and a better short-term quality of life in favour of the minimally invasive group without compromising radicality and lymph node yield.<sup>12, 13</sup> However, an increasing body of evidence suggests that minimally invasive esophagectomy carries a significant learning curve.<sup>14-18</sup> This gives rise to the question whether the results of this randomized controlled trial may be extrapolated to the general population and, if so, how can this technique safely be introduced and implemented in daily practice?

Within minimally invasive esophagectomy a variety of performance shaping factors may influence postoperative outcomes. The first thoracoscopic esophagectomy was performed with the patient in left lateral decubitus position.<sup>11</sup> To improve the exposure of the posterior mediastinum and obtain better ergonomic results, some surgeons suggested changing the left lateral decubitus position to a prone position. Nevertheless, conversion to open surgery may be easier in left lateral decubitus position.<sup>19</sup> The semiprone position, combining “the best of both worlds”, has been proposed as an alternative. Also, the use of a robotic platform may improve outcomes of this complex thoracoscopic procedure.<sup>20</sup> The three-dimensional, magnified surgical view combined with a high degree of freedom of the articulating instruments facilitates meticulous dissection from diaphragm to thoracic inlet. The use of robot-assisted minimally invasive esophagectomy may also open new indications for curative surgery in patients with T4b tumors, high mediastinal tumors and lymph node metastases after neoadjuvant treatment.

### **Postoperative morbidity**

Esophagectomy with a two-field lymphadenectomy is a major surgical procedure. Although mortality following esophagectomy steadily decreased over the past years, morbidity rates remain high compared to other elective cancer surgery.<sup>8</sup> Frequently encountered postoperative complications are anastomotic leakage (0-35%), chyle leakage (0.8-11%), and atrial fibrillation (AF) (12-37%). However, pulmonary complications, particularly pneumonia, are the most common with incidences reported up to 55%.<sup>8</sup> Pulmonary complications are associated with an increased hospital stay, an increased intensive care unit stay, and an increase

in 90-day mortality.<sup>21,22</sup> Therefore, many perioperative strategies to prevent pulmonary complications after esophagectomy have been and are still being investigated and introduced in daily clinical practice.<sup>23</sup>

Optimizing performance status of patients undergoing neoadjuvant chemoradiotherapy and esophagectomy (trimodality therapy) is one of these strategies. An optimal physical performance status may prevent postoperative morbidity. One of the factors influencing performance status during trimodality therapy is the nutritional status of the patient.<sup>24,25</sup> To achieve an optimal nutritional status, additional enteral feeding is preferred when possible and may be accomplished in various ways.<sup>26</sup> If direct oral feeding is impossible one may consider placement of a nasojejunal or a jejunostomy feeding tube. Although jejunostomy feeding tube placement may be more invasive, a nasojejunal tube may lead to a substantial degree of discomfort and will dislocate in 20 to 35% of patients after placement.<sup>26</sup> The use and timing of jejunostomy tube feeding placement during trimodality therapy is therefore under debate. Early identification of pulmonary complications after esophagectomy is of importance to timely initiate treatment. This may reduce the chance of systemic inflammatory response syndrome (SIRS) development which potentially leads to respiratory and hemodynamic instability.<sup>27</sup> The occurrence of postoperative pulmonary complications has been associated with several factors, such as sarcopenia, neoadjuvant chemoradiotherapy, chronic obstructive pulmonary disease, a poor performance status and open surgery.<sup>28-30</sup> However, also non-pulmonary postoperative complications, such as recurrent laryngeal nerve injury, may be associated with pulmonary complications.<sup>31-33</sup> During esophagectomy, thermal injury, stretching, compression, or vascular compromise of the recurrent laryngeal nerve may cause recurrent laryngeal nerve palsy. The recurrent laryngeal nerve is the most important motor nerve of the larynx and innervates the cricopharyngeal muscle which forms the upper esophageal sphincter, hereby playing a central role in swallowing.<sup>34</sup> Despite the fact that it has been shown that recurrent laryngeal nerve injury leads to an increased incidence of aspiration pneumonia after esophagectomy, it is unknown what the results are regarding long-term recovery. Another frequently encountered complication after esophagectomy is AF. Although the exact pathophysiology of new-onset AF after esophagectomy remains unclear, it is described to be associated with infectious complications. However, it remains unknown whether atrial



fibrillation could be of clinical, predictive value.<sup>35-37</sup>

One may assess the effect of interventions in order to improve outcomes after therapy once the outcomes to be studied are properly defined. The registration of postoperative pulmonary complications, particularly pneumonia, in esophageal cancer patients is hampered by a lack of a validated, uniform and widely accepted and used definition.<sup>38</sup> The wide variety of definitions used for postoperative pneumonia causes an over- or underestimation of the true incidence of pneumonia after esophagectomy.<sup>8</sup> This gap leads to the impossibility to properly assess and evaluate the effect of interventions performed in order to reduce postoperative pneumonia. To fill this gap an objective and easy applicable scoring system to define pneumonia after esophagectomy has been developed.<sup>39</sup> However, before such a definition can be used in international guidelines it requires external and international validation.

### **Neuroimmunity**

As discussed above, many factors have been associated with the occurrence of postoperative pulmonary complications. However, their exact pathogenesis is unknown. The inflammatory response is thought to be a pivotal factor, since the development of SIRS within 48 hours postoperatively is the sole independent predictor of the occurrence of later pulmonary complications.<sup>27</sup>

As an integral part of esophagectomy the vagus nerve is transected. The respiratory system is densely innervated by vagal sensory nerve fibers that regulate several autonomic functions, such as mucosal mast cell activation, mucus secretion, the breathing pattern, bronchospasm and possibly inflammation.<sup>40-42</sup> Loss of each of these functions may contribute to an increase in pulmonary injury. Recently, it has been demonstrated that it is possible to spare the pulmonary branches of the vagus nerve during thoracoscopic esophagectomy.<sup>43,44</sup> Furthermore, it has been shown that nutritional activation of the vagus nerve via dietary lipids attenuates the local and systemic inflammatory response. High-fat enteral nutrition stimulates cholecystokinin receptors centrally or peripherally by way of the afferent vagus nerve leading to inhibition of the inflammatory response by way of vagal efferents and nicotinic receptors.<sup>45</sup> However, it remains questionable whether sparing these vagal branches, and stimulating

them through lipid-enriched nutrition, influences the inflammatory response and pulmonary function following esophagectomy.

### **Thesis Outline**

The aim of this thesis is to find new strategies to reduce pulmonary complications after esophagectomy. To this regard, the current value and future influence of minimally invasive surgery are explored in part I of this thesis. In part II the focus lies on improvement of perioperative care. The value of sparing and stimulating the vagus nerve in LPS-induced acute lung injury is explored in part III.

# Research questions

## Part I. Minimally invasive surgery

- *What is the current practice of surgeons worldwide regarding esophageal cancer and what has changed since 2007 ? (chapter 2)*
- *Does minimally invasive esophagectomy improve postoperative outcomes in a population-based setting? (chapter 3)*
- *How can robotic assistance improve minimally invasive esophagectomy? (chapter 4)*
- *Is the semiprone position in minimally invasive esophagectomy safe in terms of postoperative morbidity and short-term oncological results? (chapter 5)*

## Part II. Perioperative care

- *What is the incidence and severity of jejunostomy-related complications and does jejunostomy feeding tube placement influence nutritional status, postoperative complications and long-term survival? (chapter 6)*
- *How is recurrent laryngeal nerve injury diagnosed and treated after esophagectomy and what are the associated short- and long-term results? (chapter 7)*
- *Does new-onset atrial fibrillation after esophagectomy has a predictive value for infectious complications after esophagectomy? (chapter 8)*
- *Can the Utrecht Pneumonia Score be simplified and is this scoring model a valid method to define pneumonia following esophagectomy within the Netherlands? (chapter 9)*
- *Is the Uniform Pneumonia Score a valid method to define pneumonia following esophagectomy outside the Netherlands? (Chapter 10)*

## Part III. Neuroimmunity

- *What is the anti-inflammatory function of the pulmonary branches of the vagus nerve in LPS-induced acute lung injury? (chapter 11)*
- *What is the effect of lipid enriched nutrition on the development of LPS-induced acute lung injury and what is the role of the vagus nerve in this mechanism? (chapter 12)*

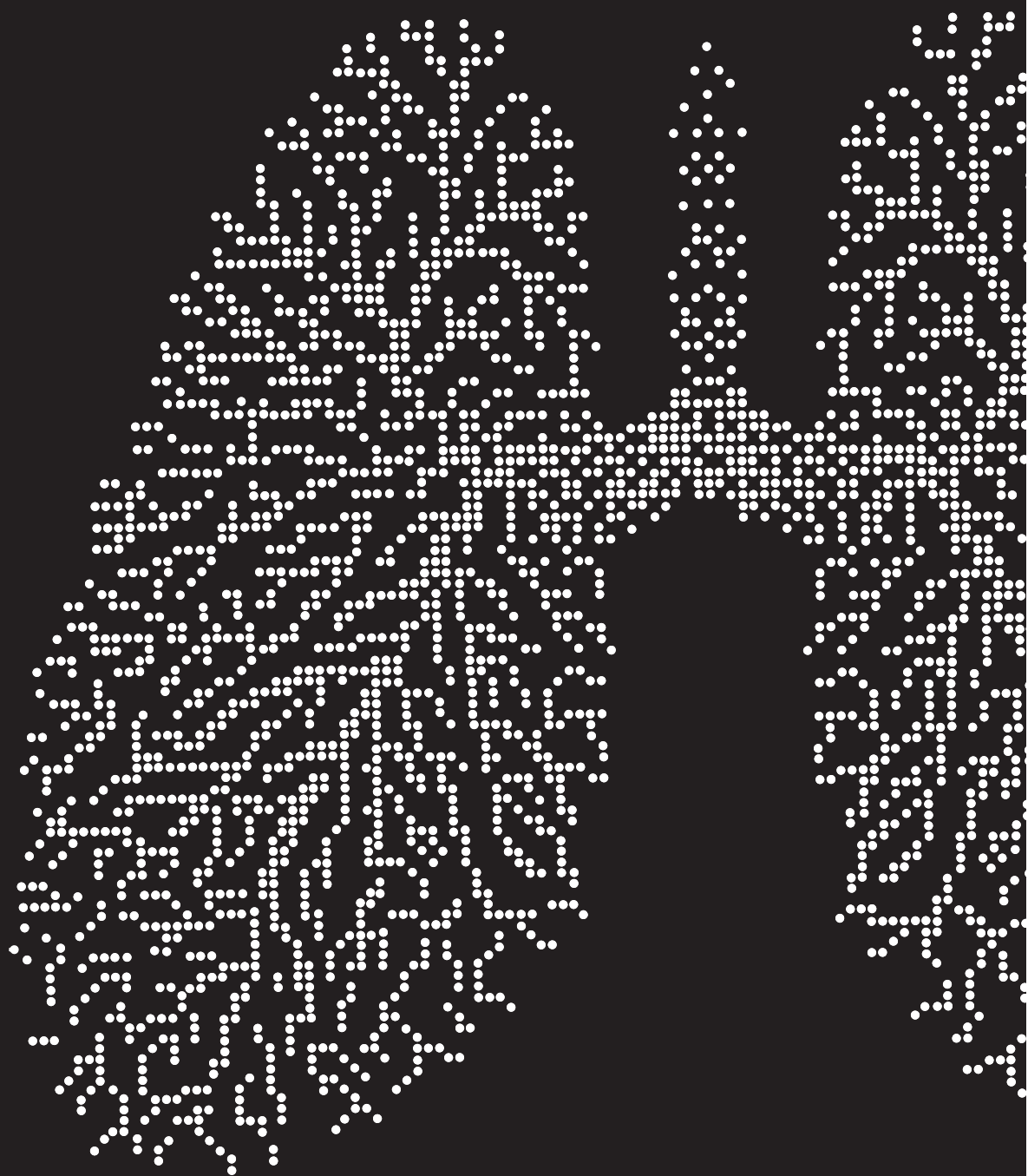
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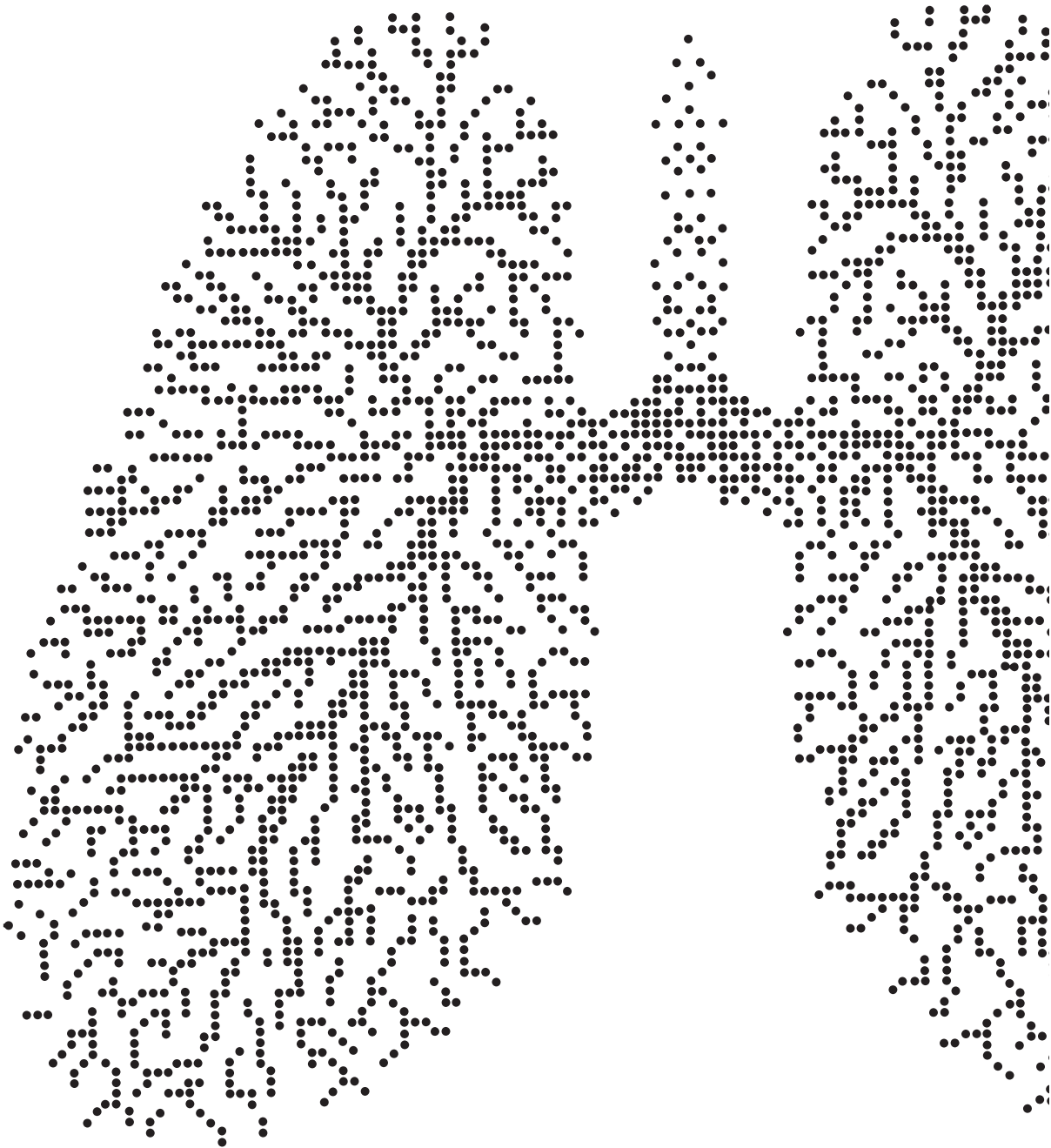






# PART I

## Minimally invasive surgery





# Chapter 2

## Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer

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*Diseases of the Esophagus. 2017 Jan 1;30(1):1-7*

## Abstract

2

**Background:** The aim of this study was to evaluate the worldwide trends in surgical techniques for esophageal cancer by comparing it to our previous survey from 2007. In addition, new questions were added for gastroesophageal junction (GEJ) cancer.

**Materials & Methods:** An international survey on surgery of esophageal and gastroesophageal junction cancer was performed amongst surgical members of the International Society for Diseases of the Esophagus, the World Organization for Specialized Studies on Disease of the Esophagus, and the International Gastric Cancer Association. Also surgeons from personal networks were contacted. The participants filled out a web based questionnaire about surgical strategies for esophageal and GEJ cancer.

**Results:** The overall response rate was 478/1147 (42%). The respondents represented 49 different countries and 6 different continents. The annual cumulative number of esophageal and gastric resections per surgeon was low ( $\leq 11$ ) in 11%, medium (11-21) in 17% and high ( $\geq 21$ ) in 72% of respondents. In a subgroup analysis of esophageal surgeons the number of high volume centers increased from 45% to 54% over the past 7 years. The preferred lymph node dissection was two-field in 86%. A gastric conduit was the preferred method of reconstruction in 95%. In 2014, the preferred approach to esophagectomy was minimally invasive transthoracic in 43%, compared to 14% in 2007. In minimally invasive transthoracic esophagectomy the cervical anastomosis was favored in 54% of respondents in 2014 compared to 87% in 2007. The preferred technique of construction of the cervical anastomosis was hand-sewn in 64% and stapled in 36%, whereas the thoracic anastomosis was stapled in 77% and hand-sewn in 23%. The preferred surgical approach for Siewert type 1 tumors (5-1 cm proximal of the GEJ) was esophagectomy in 93% of respondents, whereas 6% favored gastrectomy and 3% combined a distal esophagectomy with a proximal gastrectomy. For Siewert type 2 tumors (1-2 cm from the GEJ) an extended gastrectomy was favored by 66% of respondents, followed by esophagectomy in 27% and total gastrectomy in 7%. Siewert type 3 tumors (2-5 cm distal of the GEJ) were preferably treated with gastrectomy in 90% of respondents, esophagectomy in 6% and extended gastrectomy in 4%.

**Conclusion:** The preferred curative surgical treatment of esophageal cancer is minimally

invasive transthoracic esophagectomy with a two-field lymph node dissection and gastric conduit reconstruction. A strong worldwide trend towards minimally invasive surgery is observed. The preferred surgical treatment of GEJ tumors is esophagectomy for Siewert type 1 tumors and gastrectomy for Siewert type 3 tumors. The majority of surgeons favor an extended gastrectomy for Siewert type 2 tumors.

## Background

2

Esophageal cancer is an aggressive disease, illustrated by the annual worldwide mortality rate of approximately 406.800. The estimated incidence was 482.000 in 2008. Nowadays it is the sixth leading cause of cancer-related mortality.<sup>1,2</sup> The curative treatment for locoregional tumors of the esophagus or gastroesophageal junction (GEJ) consists of (combinations of) chemotherapy, radiotherapy and surgery. Several aspects of its surgical treatment are currently under debate. One of these topics is the introduction of thoraco-laparoscopic surgery. Open esophagectomy and gastrectomy with en bloc lymphadenectomy are associated with considerable morbidity and mortality. Minimally invasive esophagectomy and gastrectomy are associated with better postoperative outcomes, such as a reduction in complication rate, but are complex procedures with long learning curve.<sup>3</sup> Another topic of debate is whether to perform a transhiatal or transthoracic esophagectomy for distal esophageal cancer. Transhiatal esophagectomy is associated with less morbidity compared to transthoracic esophagectomy<sup>4</sup>, however, the long-term oncologic results may be inferior due to a less radical en bloc esophagolymphadenectomy.<sup>5</sup> Regarding the esophagogastrostomy, some surgeons prefer an intrathoracic location, whereas others favor a cervical anastomosis. Furthermore, a hand-sewn anastomosis is preferred by some surgeons, whereas others favor the stapled technique.<sup>6</sup>

A distinct entity in upper gastrointestinal surgery are Gastroesophageal junction (GEJ) tumors. These can be categorized by means of the TNM7 system, in which the tumors are recognized and staged according to either the esophageal or gastric classification.<sup>7</sup> Also, Siewert and colleagues have classified the location of the GEJ tumors into type I (1-5 cm proximal to the GEJ), type II (1 cm proximal - 2 cm distal to GEJ), and type III (2-5 cm distal to GEJ).<sup>8</sup> It is generally assumed that Siewert type I tumors are treated with esophagectomy, whereas Siewert type III tumors should be resected by means of gastrectomy. However, no clear treatment strategy exists for Siewert type II tumors.<sup>9,10</sup>

In 2007 a worldwide survey on preferences in the surgical treatment of esophageal tumors was conducted to provide an insight in the surgical preferences at that time.<sup>11</sup> The objective of the current survey was to evaluate the current surgical practice and to identify trends. In addition, new questions were added for gastroesophageal junction cancer. A secondary aim was to assess the differences between the preferences of surgeons from different continents.

## Materials & Methods

A cross-sectional international survey was carried out to evaluate the preferences in surgery for cancer of the esophagus or GEJ. Invitations for the English web-based survey were sent to 351 members of the International Society for Diseases of the Esophagus (ISDE), 152 members of the World Organization for Specialized Studies on Disease of the Esophagus (OESO) and 615 members of the International Gastric Cancer Association (IGCA). The members of the IGCA were only questioned about surgery for GEJ tumors, not esophageal tumors. The associations gave their approval for the distribution of the survey invitations. Also, the questionnaire was forwarded to 29 Dutch gastroesophageal surgeons from the network of the investigators (JPR, RvH). The invitations for participation were sent in July 2013 (ISDE & OESO) and in September 2013 (IGCA). A total of 2 monthly reminders were sent to the members that did not respond. The surveys were also distributed at the 12th OESO World Congress in Paris and the 11th Congress of the European Society for Diseases of the Esophagus in Rotterdam. In case the surgeons were members of more of these associations, they were requested to fill in the survey only once. The records of the respondents were checked by hand, based on name, email-address, and IP-address for any duplicates. In case of duplicate records, only the initial response was included. The survey was closed January 31st 2014.

The survey consisted of questions about demographics, preferences for diagnosis, classification, and treatment. The adenocarcinomas of the GEJ were divided into type 1, 2, and 3 according to the Siewert classification.<sup>8</sup> Subgroup analyses were made between surgeons' volume and continent. The contribution of Africa and Oceania was <5% of the total response, so these continents were not included in the subgroup analysis. Percentages were presented as values rounded to the nearest integer, so no decimals are shown in the text.

## Results

2

### Demographics

The survey was filled out by 248/615 respondents from the IGCA and 230/532 respondents from the OESO and ISDE . Therefore, the overall response rate was 42% (478/1147). The respondents represented 49 different countries and 6 continents (table 1). The majority (65%) of the respondents indicated that they worked in a university hospital. The reported annual cumulative number of esophageal and gastric resections was low ( $\leq 11$ ) in 11%, medium (11-21) in 17% and high ( $\geq 21$ ) in 72% of respondents. With respect to continent, 60% of respondents from Asia perform high volume surgery. Europe, South America and North America are showing lower percentages of high volume surgery, respectively 32%, 23% and 16%.

**Table 1.** Respondents per country

	Respondents (N= 435)	(%)
<b>Asia</b>	<b>166</b>	<b>38.2</b>
Japan	78	17.9
China	29	6.7
South Korea	27	6.2
India	9	2.1
Hong Kong	6	1.4
Russia	4	0.9
Singapore	3	0.7
Taiwan	3	0.7
Thailand	3	0.7
<b>Europe</b>	<b>141</b>	<b>32.4</b>
Italy	32	7.4
Netherlands	24	5.5
United Kingdom	13	3.0
Turkey	10	2.3
Spain	7	1.6
Germany	7	1.6
Portugal	6	1.4
Greece	6	1.4
France	5	1.1
Poland	5	1.1
Romania	4	0.9



**Table 1 continued.** Respondents per country

	Respondents (N= 435)	(%)
Ukraine	4	0.9
Belgium	3	0.7
Czech Republic	3	0.7
<b>North America</b>	<b>57</b>	<b>13.1</b>
United States of America	43	9.9
Canada	9	2.1
Costa Rica	4	0.9
<b>South America</b>	<b>57</b>	<b>13.1</b>
Brazil	36	8.3
Chile	8	1.8
Argentina	7	1.6
<b>Oceania</b>	<b>8</b>	<b>1.8</b>
Australia	8	1.8
<b>Africa</b>	<b>6</b>	<b>1.4</b>
Egypt	3	0.7

*Legend.* Distribution of respondents per continent. Countries with  $\geq 3$  respondents are specified.

## Esophageal cancer

For tumors of the esophagus the minimally invasive transthoracic approach was preferred in 43%, followed by the open transthoracic approach (38%), the open transhiatal approach (15%), and the minimally invasive transhiatal approach (4%). This means a 3-fold increase in the number of respondents favoring the minimally invasive technique since 2007 (figure 1, table 2). Also, an increase in the case volumes of esophageal resection per respondent was seen (figure 2). The high-volume respondents preferred the minimally invasive esophagectomy more frequently than the low-volume respondents. In conventional open surgery 93% of respondents performed a right-sided thoracotomy in 2014, which is comparable to 2007 (table 2). In Europe and North America a greater majority preferred a 2 field lymph node dissection, whereas in Asia both the two-field and three-field lymph node dissections were reported almost equally (figure 3). A 3-field lymph node dissection was performed in 15% of high-volume surgeons compared to 6% of low-volume surgeons.

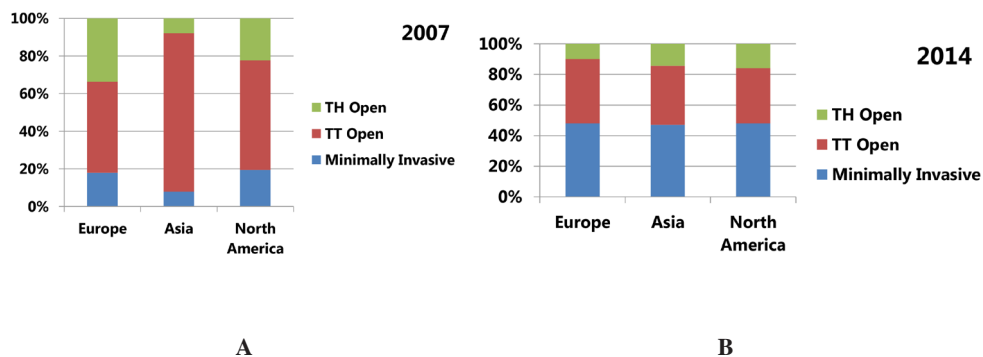
The preferred method of reconstruction was a gastric conduit in 95%. In case a gastric conduit was favored, the staple line was oversewn in 68% of respondents. Less favorite reconstructions were jejunal interposition (3%), colonic interposition (2%), and whole stomach (1%). Sixty-eight % of respondents favor an intrathoracic anastomosis over an cervical anastomosis for an open transthoracic esophagectomy, this is an increase as compared to 2007 (Figure 4, table 2). Also for minimally invasive transthoracic surgery a trend towards intrathoracic anastomosis was seen. (figure 4, table 2). The technique of the cervical anastomosis was preferably hand-sewn by 71% of respondents from Europe, 57% from Asia, and 69% from South America, whereas 56% of respondents from North America preferred the stapled technique. In contrast, the majority (77%) of respondents from all continents favor the stapled technique for the intrathoracic anastomosis.

**Table 2.** Comparisons of results for esophageal cancer with the survey of 2007<sup>11</sup>

	2007	2014
Respondents	47%	42%
High volume Centres	45%	54%
TT MIE	14%	43%
Open TTE	52%	38%
Open THE	26%	15%
TH MIE	0%	4%
No preferred approach	8%	0%
Right-sided thoracotomy	91%	93%
Intrathoracic anastomosis (open TTE)	44%	68%
Cervical anastomosis (open TTE)	56%	32%
Intrathoracic anastomosis (TT MIE)	15%	46%
Cervical anastomosis (TT MIE)	85%	54%
1 field lymph node dissection	12%	1%
2 field lymph node dissection	70%	86%
3 field lymph node dissection	16%	11%
No lymph node dissection	2%	2%

**Abbreviations.** TTE: transthoracic esophagectomy, THE: transhiatal esophagectomy

MIE: minimally invasive esophagectomy. TT: transthoracic, TH: Transhiatal

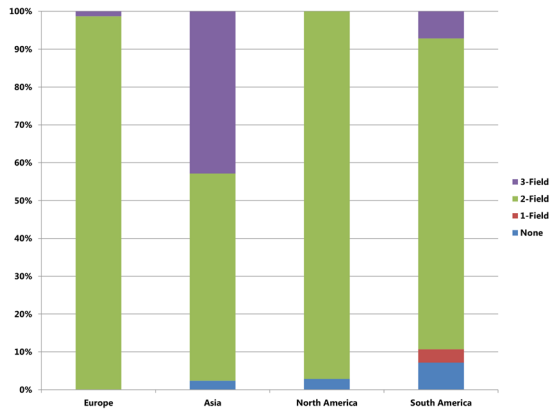


**Figure 1.** Surgical approach by continent in 2007 (A) and 2014 (B).

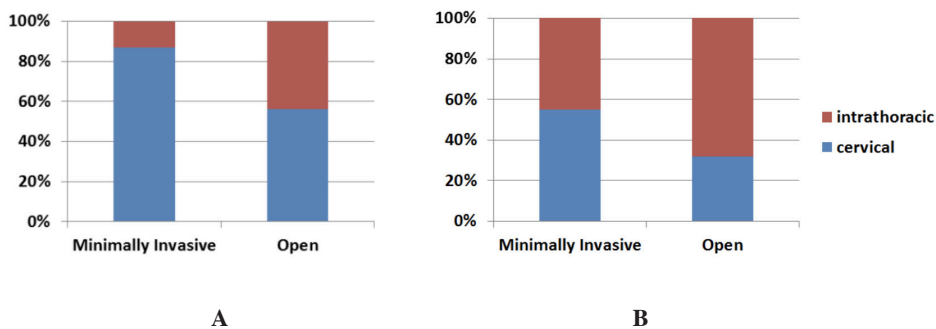
*Abbreviations: TT: transthoracic, TH: Transhiatal*



**Figure 2.** Surgeon's volume.



**Figure 3.** Preferred lymph node dissection per continent.



**Figure 4.** Preferred location of anastomosis for transthoracic procedures in 2007 (A) and in 2014 (B).

## GEJ cancer

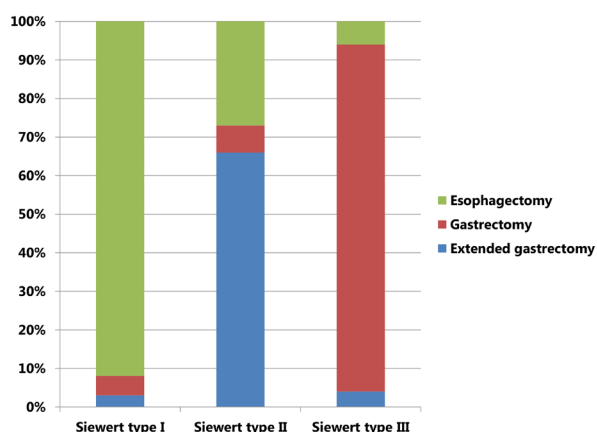
### *Diagnosis and classification*

For choosing the optimal treatment for GEJ tumors, adequate determination of tumor location is pivotal because the location affects the surgical procedure. Esophagogastroscope was deemed most important by 81% of respondents, followed by CTscan in 14%, EUS in 2%, PETscan in 1%, and diagnostic laparoscopy in 1%. The Siewert classification was used solely by 39%, the TNM7 by 16%, whereas 45% of respondents indicated that they used both the Siewert classification and the TNM7 classification.

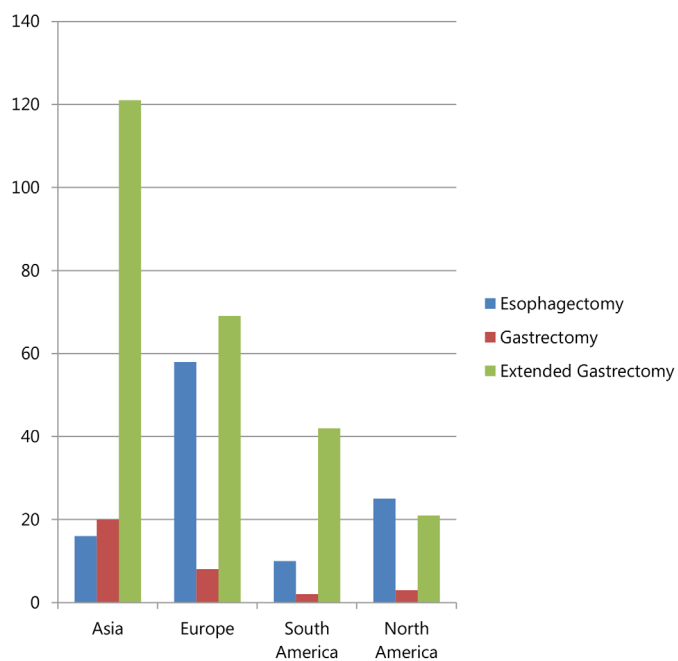
### Treatment

The preferred surgical approach for Siewert type I tumors was an esophagectomy, Siewert type III tumors were preferably treated with gastrectomy (figure 5). For Siewert type II tumors a combined distal esophagectomy and (extended) proximal gastrectomy, defined as the resection of the proximal stomach and the distal third of the esophagus was favored by 66% of respondents, followed by esophagectomy and total gastrectomy in (figure 5). The surgeons with low or medium annual case volumes preferred an esophagectomy more often than high volume surgeons with regard to Siewert type II tumors (figure 6) According to the respondents the initial surgical strategy for all GEJ tumors was estimated to alter during the actual surgery at an average of 10%. Interestingly, the surgeons who indicated that they only performed esophagectomies have rarely favored the option of gastrectomy for Siewert type II tumors (figure 7), while they did select this option for Siewert type III tumors. Also, the gastric surgeons who did not perform esophagectomies, seldomly preferred esophagectomy for Siewert type II tumor, whereas they did for type I tumors.

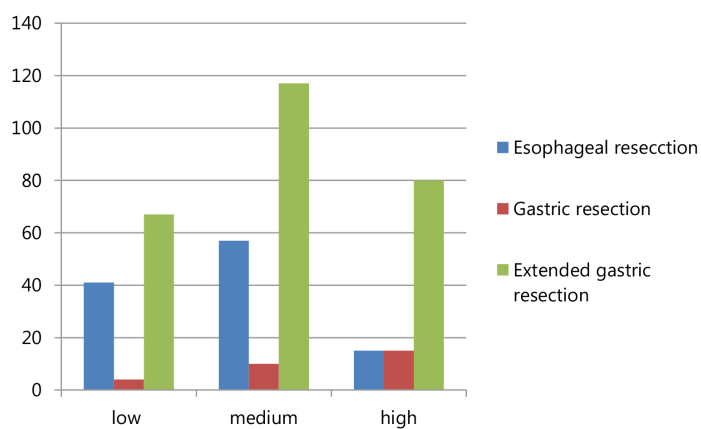
Concerning lymph node dissection, the majority of the respondents who performed an esophagectomy for GEJ tumors preferred a two-field dissection. (figure 8a). The respondents who perform a gastrectomy for GEJ tumors favored a D2 lymph node dissection (figure 8b).



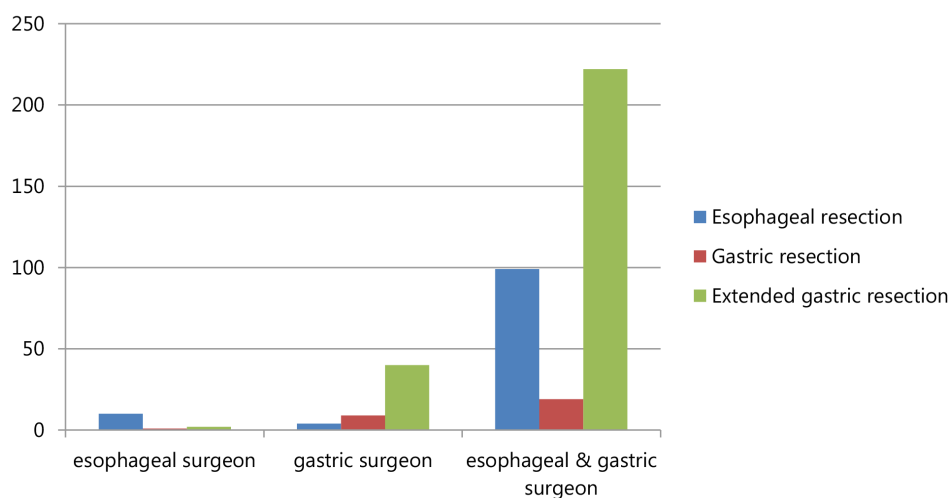
**Figure 5a.** Preferred surgical treatment of Siewert type 2 tumors.



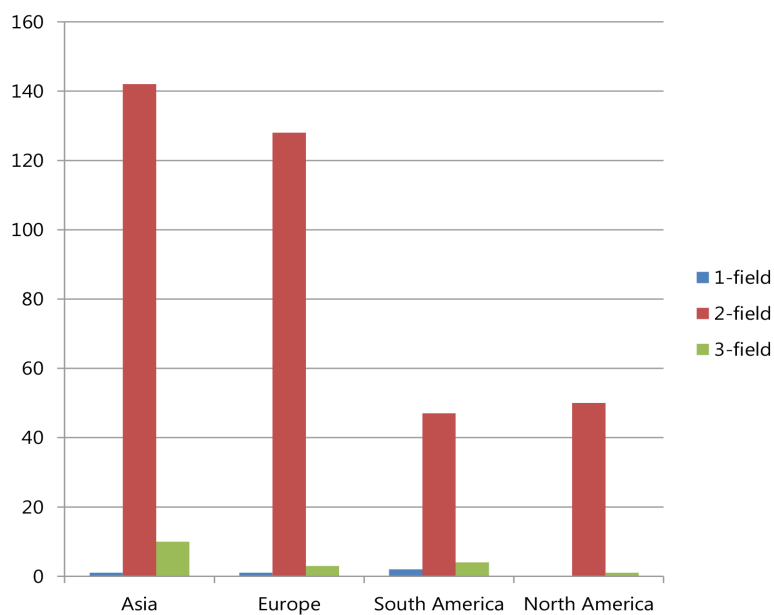
**Figure 5b.** Preferred surgical treatment (in numbers) of Siewert type 2 tumors, categorized by continent.



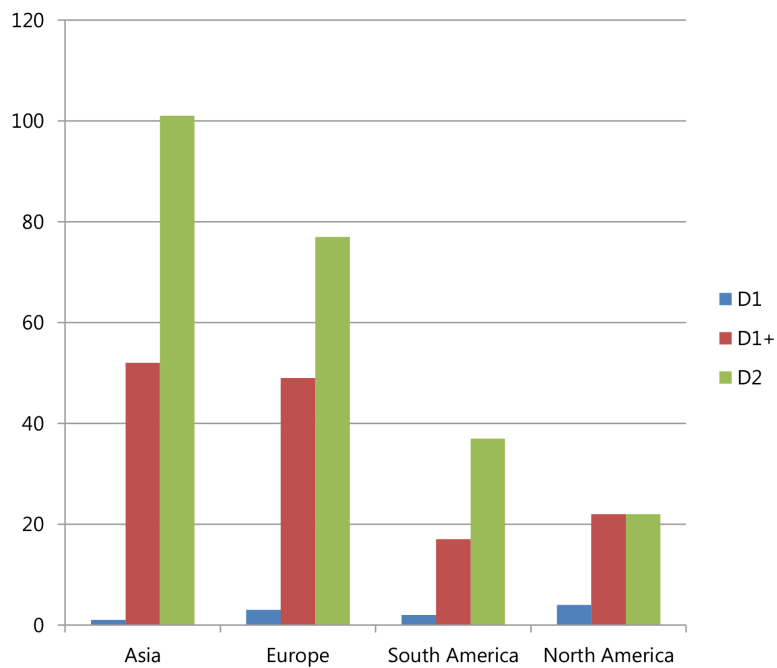
**Figure 6.** Number of respondents favoring the different surgical treatments of Siewert type 2 tumors sorted by annual case volume: low ( $\leq 30$ ), medium (31-59), and high ( $\geq 60$ ).



**Figure 7.** Number of respondents preferring the different surgical approaches for Siewert type 2 tumors.



**Figure 8a.** Number of respondents preferring different types of lymph node dissection for esophagectomy in patients with an GEJ tumor.



**Figure 8b.** Number of respondents preferring different types of lymph node dissection for gastrectomy in patients with a GEJ tumor.



## Discussion

In this study the current worldwide trends in esophageal and gastro-esophageal junction surgery for cancer were evaluated by means of a survey amongst gastroesophageal surgeons. The results were compared to the survey conducted in 2007 to analyze trends. In addition, new questions were added for gastroesophageal junction cancer. It was found that a transthoracic esophagectomy with two-field lymph node dissection and gastric conduit reconstruction was the preferred procedure to resect esophageal cancer. An increase in popularity of minimally invasive esophagectomy was seen, especially amongst high volume surgeons. Furthermore, this international survey has a specific focus on the surgical treatment of GEJ tumors, since no general agreement on various aspects of its surgical treatment has been established. Therefore, an overview of the preferences of international upper gastrointestinal surgeons provides an important insight in current practice. This study showed that both extended gastrectomy and esophagectomy are generally accepted treatments for Siewert type II tumors.

This study reflects the professional opinion of a substantial part of the international upper gastro-intestinal surgeons. By contacting all surgical members of the major esophageal and gastric cancer societies both fields of expertise are represented. All participants received identical questionnaires as in 2007 to ensure consistency in results. By excluding duplicates from overlapping memberships, the quality of the answers was improved. The response rate of 42% indicates that this survey is a partial representation of worldwide practice. This response rate might introduce a bias since a selected group of surgeons may have responded. However, the response rate is comparable to the rate of the survey conducted in 2007. Also, it needs to be taken into account that the members of the participating societies form a sample of the surgeons worldwide. Not all surgeons are members of these societies, introducing another bias. Inevitably, this study evaluates expert opinions rather than objective measures, which should be taken into account before generalizing these findings.

### Esophagus

Comparing the results of this survey for esophageal surgery to our previous survey from 2007,<sup>11</sup> an increase in the case volumes of esophageal resection per respondent was seen.

Most probably this trend will continue, considering that still 25% of the respondents were low-volume surgeons (<11 esophageal resections per year) in 2014. The number of surgeons performing low-volume or medium-volume esophageal resections are expected to decrease, since studies have shown the influence of high-volume esophageal surgery on postoperative morbidity and mortality.<sup>12-15</sup> It might even be argued that the threshold for high-volume resection (>21 esophageal resections per year) is relatively low. The numbers for low and high volume were deliberately chosen to match our previous survey from 2007 and reflect the cut-off point for esophageal surgery in the Netherlands. By choosing the same cut off values we were able to identify possible trends in surgical techniques. However, we feel that a true high volume center might perform over 50 or even 100 esophagectomies per year.

Furthermore, the trend towards minimally invasive surgery was found in all continents and is in line with systematic reviews and meta-analyses indicating advantages of minimally invasive esophagectomy, such as reduced blood loss, post-operative (pulmonary) complication rate, and hospital stay, compared to open esophagectomy.<sup>16, 17</sup>

The preferred lymph node dissection was two-field in Europe, North America, and South America compared to an equal distribution between two- and three-field in Asia. A recent meta-analysis demonstrated that more lymph nodes were retrieved in the East, defined as Asia, compared to the West, defined as Europe, Australia, and North America.<sup>18</sup> Literature shows that surgeons performing minimally invasive esophagectomy were able to perform equally adequate 2- and 3-field lymph node dissections, compared to open esophagectomy.<sup>18</sup> Concerning the long-term oncologic outcomes of minimally invasive esophagectomy, evidence is still lacking. Radicality percentages and lymph node retrieval were demonstrated to be equal, but no comparative data on survival exist to date.<sup>3</sup> No difference between 2007 and the current survey concerning the preferred extent of lymph node resection was seen. The preferred type of reconstruction is a gastric conduit. In the previous survey from 2007, a whole stomach was used more often, especially by surgeons from Asia and North America and more experienced surgeons.<sup>11</sup> This is a positive development, since literature shows that a gastric conduit is accompanied by less complaints of dysphagia, a better quality of life and

possibly increased survival rates.<sup>19</sup>

With regard to the anastomosis a trend in favor of intrathoracic anastomosis after open trans-thoracic esophagectomy was seen. This preference for the intrathoracic anastomosis can possibly be explained by an association with more evidence about a lower leak rate and less recurrent nerve trauma.<sup>20</sup> Furthermore, there was an increase in applying a stapled intrathoracic anastomosis instead of a hand-sewn intrathoracic anastomosis. This might be due to the overall increase in experience with minimally invasive techniques in which staplers are used frequently. However, evidence on the optimal location and technique of the anastomosis is not conclusive.<sup>20</sup>

### **GEJ cancer**

Regarding GEJ tumors, results of this study show a preference for esophagectomy for Siewert type I tumors and gastrectomy for Siewert type III tumors. For Siewert type II tumors both extended gastrectomy and esophagectomy were frequently used. In Asia the extended gastrectomy was more popular, whereas in North America the majority of respondents favored esophagectomy. The preferred lymph node dissection was two-field for esophagectomy and D2 for gastrectomy. Even though the diagnostic accuracy of the location of the GEJ tumors is limited to 70%.<sup>21</sup> Only 10% of the initial surgical approaches is estimated to be converted to another procedure. This survey indicated that high volume surgeons treated Siewert type II tumors more frequently by means of extended gastric resection rather than esophageal resection.

The wide variety in surgical treatment of Type 2 GEJ tumors illustrates that there is a need for clear evidence based guidelines. Future prospective studies should evaluate the optimal surgical procedure for GEJ type II, preferably by means of a randomized controlled trial. Moreover, patients with GEJ tumors should be treated in a center that provides both esophageal and gastric surgery. Since GEJ tumors are located at the transitional area between the esophagus and stomach, the surgical team has to be capable of performing both procedures.

## Conclusion

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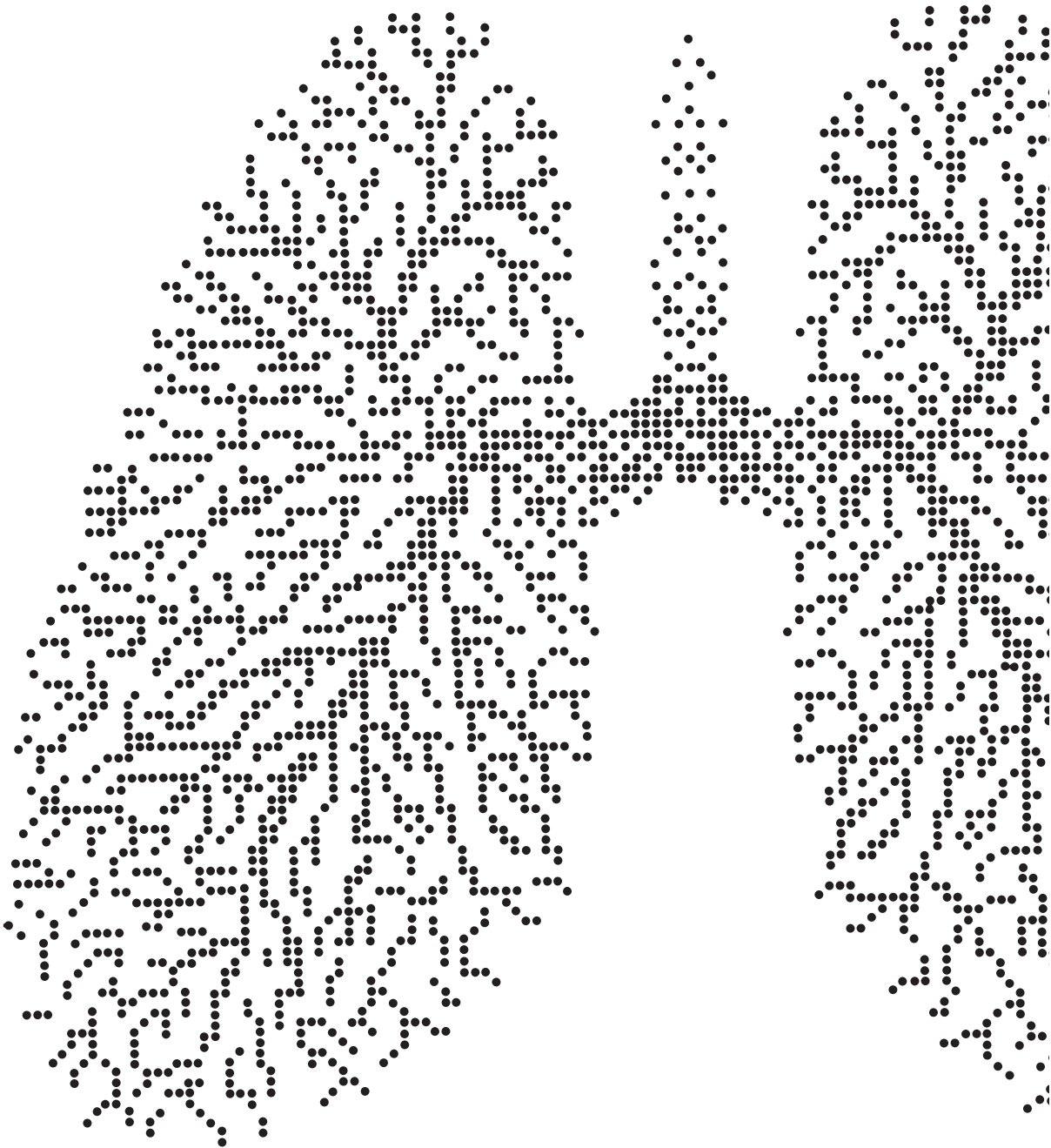
Regarding esophageal surgery a worldwide increase in minimally invasive esophagectomy was observed in this study. Furthermore, there seems to be a rise in high-volume centers for esophagectomy. Differences between continents were found with regard to extent of lymph node dissection and location of the anastomosis. With regard to GEJ cancer there is a need for clear evidence based guidelines, mainly for type II GEJ tumors. For that purpose a randomized trial is proposed.

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# Chapter 3

## A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands

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## Abstract

**Background:** Randomized controlled trials and cohort studies have shown that minimally invasive esophagectomy (MIE) is associated with reduced pulmonary complications and shorter hospital stay as compared to open esophagectomy (OE). The aim of this study was to compare OE with MIE in a population based setting.

**Material & Methods:** Patients who underwent transthoracic esophagectomy for cancer between 2011 and 2015 were selected from the national Dutch Upper GI Cancer Audit. Excluded were hybrid, transhiatal and emergency procedures. Patients who underwent OE were compared with those treated by MIE. Propensity score matching was used to correct for differences in baseline characteristics. The primary endpoint was postoperative pulmonary complications, secondary endpoints were morbidity, mortality, convalescence and pathology.

**Results:** Some 1727 patients were included. After propensity score matching the percentage of patients with one or more complications was 62.6% after OE (N=433) and 60.2% after MIE (N=433) (p=0.468). Pulmonary complication rate did not differ between groups: 34.2% (OE) versus 35.6% (MIE) (p=0.669). Anastomotic leak- (15,5% versus 21,2%, P=0.028) and reintervention rates (21.1% versus 28.2%, P=0.017) were higher after MIE. Mortality was 3.0% in the OE group and 4.7% in the MIE group (p=0.209). Median hospital stay was shorter after MIE (14 versus 13 days, p=0.001). Percentages of R0 resections (93%) did not differ between groups. The median (range) lymph node count was 18 (2-53) (OE) versus 20 (2-52) (MIE) (P<0.001).

**Conclusion:** This population based study showed that mortality and pulmonary complications were similar for OE and MIE. Anastomotic leaks and reinterventions were more frequently observed after MIE. MIE was associated with a shorter hospital stay.

## Background

Esophageal cancer is the eighth most common cancer globally, and its incidence is increasing.<sup>1,2,3</sup> Surgical resection with radical lymphadenectomy following neoadjuvant chemotherapy or chemoradiation is regarded as the standard of care for patients with resectable locally advanced esophageal or gastroesophageal junction cancer.<sup>4,5,6</sup> Esophagectomy is a complex procedure and morbidity and mortality can be significant.<sup>7</sup> Minimally invasive esophagectomy (MIE), using a combined thoracoscopic and laparoscopic approach, was introduced in 1992 to reduce morbidity and mortality.<sup>8</sup> The feasibility, safety and possible advantages of MIE have been demonstrated in many studies in selected cohorts of patients.<sup>9-12</sup>

However, only one randomized controlled trial comparing OE with MIE has been published. This study demonstrated a reduced rate of pulmonary complications, decreased blood loss and better health related quality of life for patients after MIE.<sup>10-12</sup> As a result of this, MIE has gained popularity in the last decade.<sup>13</sup> Although MIE is expected to be beneficial to most patients, the widespread implementation of MIE might have come at the cost of patient safety.<sup>14,15</sup> Therefore, the aim of our study was to compare OE with MIE in terms of morbidity, mortality, convalescence after surgery and pathology in a population based setting.

## Materials & Method

### Dutch Upper Gastrointestinal Cancer Audit

3 Since 2011 all patient undergoing curative resection for esophageal or gastric cancer in the Netherlands are registered in the Dutch Upper Gastrointestinal Cancer Audit (DUCA).<sup>16</sup> The aim of this nationwide registration is to monitor, standardize and improve the quality of esophageal cancer care. Participation in the DUCA is obligatory for all hospitals performing esophagectomies and gastrectomies for epithelial cancers. Process, structure and outcome parameters are defined and feedback is given to the participating centers at regular intervals for steering information and benchmarking. Data on patient characteristics (age, sex, ASA status, comorbidities), disease characteristics (diagnostic tests, tumor stage), surgical and non-surgical treatment, outcome parameters (including complications, length of hospital stay, intensive care unit (ICU) stay, reinterventions and readmissions) are registered by each hospital via a web based platform. Detailed descriptions of definitions used in the registry were provided via an information button in the online registry program to ensure uniform data registration. For the purpose of this study, patients were selected from the DUCA database.

### Patients

Patients who underwent a transthoracic esophagectomy with a two-field lymphadenectomy for cT1-4a N0-3 M0 esophageal- or gastroesophageal junction cancer between 2011 and 2015 were included. Participation in the DUCA is obligatory hence all hospitals in the Netherlands performing esophago-gastric surgery are included. Only patients who underwent a combined thoracoscopic and laparoscopic esophagectomy were included in the MIE group. In the open group, the thoracic and the abdominal phase were performed via a thoracotomy and laparotomy. Only three-stage McKeown (anastomosis in the neck) or two-stage Ivor Lewis procedures (anastomosis in the chest) with a two-field lymph node dissection and gastric conduit reconstruction were selected. Patients who underwent a hybrid or transhiatal procedure were excluded as well as patients with an American Society of Anesthesiologists (ASA) IV status or patients who underwent emergency surgery. When the operations started as a MIE and it was converted to open, the procedure was still counted as a MIE. This study was approved by the scientific committee of the DUCA and ethical approval and informed consent was waived by the committee.

## Outcomes

Information on diagnostics, intra operative data, adverse events, length of hospital stay, intensive care unit (ICU) stay, reinterventions and readmissions was retrieved from the DUCA database. The primary outcome was postoperative pulmonary complications, which were defined as clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome (ARDS) or reintubation. Secondary outcomes included clinically or radiologically proven anastomotic leakage, chylothorax, cardiac complications, postoperative bleeding, wound infection, fascial dehiscence, intra-abdominal abscess, gastric conduit necrosis, recurrent laryngeal nerve injury. Furthermore, reinterventions, defined as surgical procedures, radiological (percutaneous) interventions or endoscopic interventions, 30-day or in-hospital postoperative mortality, intensive care unit (ICU) stay, hospital stay and the number of readmission were also included as secondary outcome measures. Since the DUCA does not reveal the names of the hospitals where patients underwent their surgery due to anonymity reasons, specific data on a possible learning curve could not be obtained.

## Statistical analysis

To minimize the effect of confounding influences of measured covariates on the assessed outcome between the two study groups (OE versus MIE), propensity score matching was performed. First, a propensity score for each patient was calculated using a logistic regression model which was fitted for type of surgery using the variables listed in Table 1. Next, one-to-one matched study groups were created using nearest-neighbor (greedy) matching without replacement. To prevent poor matches, a caliper of 0.25 multiplied by the standard deviation of the logit of the propensity score was used. Covariate balance of the matched cohort was assessed using the mean standardized differences, with differences less than 10% and close to 0% taken to indicate good balance.

For subgroup analyses on the effect of the location of anastomosis on anastomotic leakage the unmatched dataset was divided into two datasets, one containing only Ivor Lewis procedures and one containing only McKeown procedures. Subsequently, the two study groups were matched in both datasets using propensity score matching as described above. Statis-

tical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (<http://www.R-project.org>; ‘MatchIt’ and ‘optmatch’ packages). A p-value of  $<0.05$  was considered statistically significant.

## Results

### Patients

A total of 2202 patients underwent a transthoracic esophagectomy with a two-field lymph node dissection and gastric reconstruction with curative intent in the Netherlands between 2011 and 2015. Some 1727 patients were included in the study (figure 1). The OE group contained 500 patients and the MIE group 1227 patients. Patient characteristics are shown in table 1. The differences in baseline characteristics between the OE and the MIE group were statistically significant across most covariates prior to adjusting, however these differences were all eliminated after adjusting with propensity score matching (Table 1). Median (range) age of the patients was 64 (34-84) years, with 66 % of patients having an ASA II status and 72% of the patients were diagnosed with a cT3 tumor. In more than half of patients a cervical esophagogastric anastomosis was created. Figure 2 illustrates that the percentage of MIE increased between 2011 (42%) and 2015 (84%).

**Table 1.** Patient and treatment-related characteristics in relation to surgical procedure

		Before Matching					After Matching				
Characteristic		OE (N =500 )		MIE (N=1227)		p value	OE (N = 433 )		MIE (N = 433)		p value
		n		n			n		n		
Gender	Female	120	24.0%	269	21.9%	0.349	98	22.6%	98	22.6%	1.000
	Male	380	76.0%	958	78.1%		335	77.4%	335	77.4%	
Age (years)		63,4	±8.6	64,0	± 8.9		64	± 8.7	64,0	± 9.0	0.561
BMI (kg/m2)		25,9	±4.2	25,4	±4.3		25,3	±4.3	25,5	±4.1	0.985
ASA score	I	70	14.0%	230	18.7%	0.052	65	15.0%	80	18.5%	0.365
	II	332	67.0%	756	61.6%		287	66.3%	271	62.6%	
	III	98	19.6%	241	19.6%		81	18.7%	82	18.9%	
Pulmonary comorbidity	No	427	84.4%	1036	84.4%	0.613	371	85.7%	375	86.6%	0.694
	Yes	73	14.6%	191	15.6%		62	14.3%	58	13.4%	
Cardiac comorbidity	No	371	74.2%	968	78.9%	0.034	325	75.1%	325	75.1%	1.000
	Yes	129	25.8%	371	30.2%		108	24.9%	108	24.9%	
Vascular comorbidity	No	322	64.4%	790	64.4%	0.995	280	54.7%	279	64.4%	0.943
	Yes	178	35.6%	437	35.6%		153	35.3%	154	35.6%	
Diabetes mellitus	No	419	83.8%	1069	81.1%	0.070	368	85.0%	370	85.5%	0.848
	Yes	81	16.2%	158	12.9%		65	15.0%	63	14.5%	

**Table 1 continued.** Patient and treatment-related characteristics in relation to surgical procedure

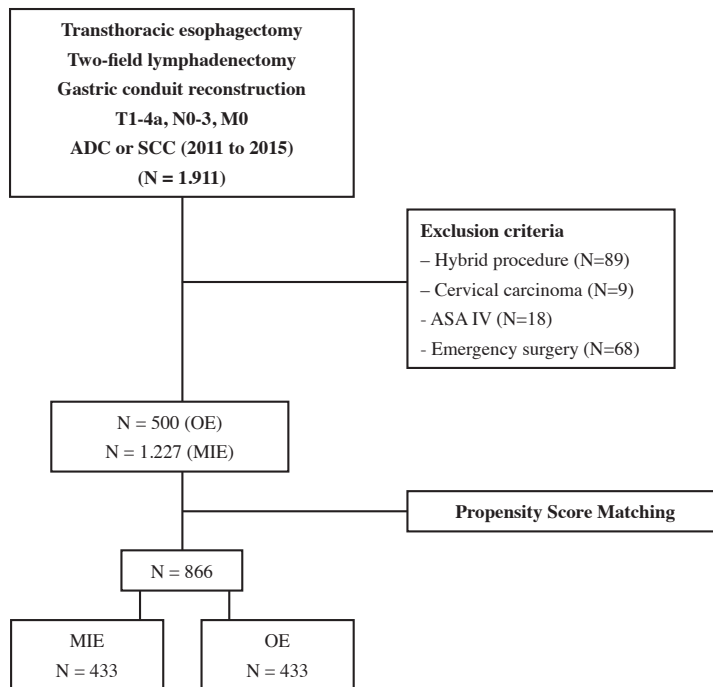
		Before Matching					After Matching				
<b>Histology</b>	AC	342	68.4%	974	79.4%	<0.001	311	71.8%	305	70.4%	0.653
	SCC	158	31.6%	253	20.6%		122	28.2%	128	29.6%	
<b>cT stage</b>	T1	27	5.4%	69	5.6%	0.008	24	5.5%	26	6.0%	0.678
	T2	84	16.8%	260	21.2%		81	18.7%	86	19.9%	
	T3	364	72.8%	872	71.1%		311	71.8%	310	71.6%	
	T4	25	5.0%	26	2.1%		17	3.9%	11	2.5%	
<b>cN stage</b>	N0	157	31.4%	461	37.6%	0.001	144	33.3%	132	30.5%	0.277
	N1	211	42.2%	530	43.2%		175	40.4%	202	46.7%	
	N2	113	22.6%	209	17.0%		97	22.4%	87	20.1%	
	N3	19	3.8%	27	2.2%		17	3.9%	12	2.8%	
<b>Location of tumor</b>	proximal	11	2.2%	14	1.1%	<0.001	8	1.8%	8	1.8%	0.916
	middle	117	23.4%	161	13.1%		98	22.6%	91	21.0%	
	distal	296	59.2%	837	68.2%		258	59.6%	259	59.8%	
	GEJ	76	15.2%	215	17.5%		69	15.9%	75	17.3%	
<b>Neoadjuvant treatment</b>	No	43	8.6%	43	3.5%	<0.001	36	8.3%	37	8.8%	0.993
	Chemo-therapy	49	9.8%	25	2.0%		21	4.8%	21	4.8%	
	Chemo-radio-therapy	408	81.6%	1117	91.0%		376	86.8%	375	86.6%	
<b>Location of anastomosis</b>	Cervical	318	63.6%	604	49.2%	<0.001	274	63.3%	289	66.7%	0.285
	Intrathoracic	182	36.4%	623	50.8%		159	36.7%	144	33.3%	
<b>Year of surgery</b>	2011	115	23.0%	88	7.2%	<0.001	73	16.9%	66	15.2%	0.623
	2012	107	21.4%	185	15.1%		94	21.7%	90	20.8%	
	2013	119	23.8%	221	18.0%		109	25.2%	118	27.3%	
	2014	81	16.2%	335	27.3%		79	18.2%	68	15.7%	
	2015	78	15.6%	398	32.4%		78	18.0%	91	21.0%	
<b>Hospital volume*</b>	0-20	81	16.2%	30	2.4%	<0.001	54	12.5%	19	4.4%	0.807
	21-40	231	46.2%	530	43.2%		204	47.1%	261	60.3%	
	41-60	84	16.8%	295	24.0%		80	18.5%	96	22.2%	
	61-80	78	15.6%	130	10.6%		69	15.9%	18	4.2%	
	81-100	26	5.2%	242	19.7%		26	6.0%	39	9.0%	

**Legend.** Data are n (%), median (range) and mean ( $\pm$ SD),

**Abbreviations.** ASA: American Society of Anesthesiologists, BMI: body mass index AC = adenocarcinoma, SCC: squamous cell carcinoma, OE = open esophagectomy, MIE = minimally invasive esophagectomy,

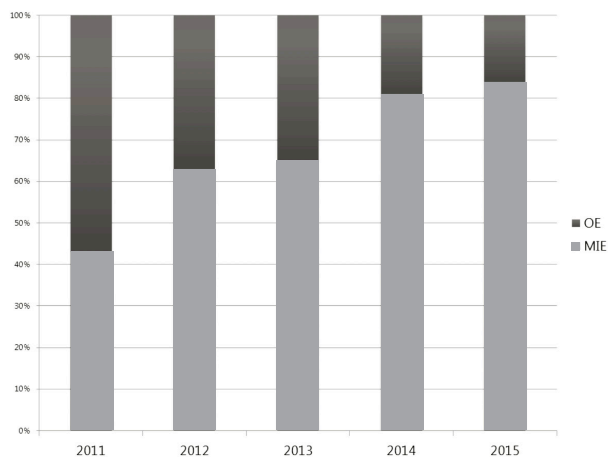
\* number of esophageal resections per year.





**Figure 1.** Flowchart

**Abbreviations:** ASA: American Society of Anesthesiologists, OE: open esophagectomy, MIE: minimally invasive esophagectomy.



**Figure 2.** Implementation of MIE in the Netherlands

**Abbreviations:** OE: open esophagectomy, MIE: minimally invasive esophagectomy.

## Outcomes

The primary outcome measure, postoperative pulmonary complications, did not differ between groups: 148 of 433 patients (34.2%) of the OE group and 154 of 433 (35.6%) patients in the MIE group had a pulmonary complication ( $p=0.669$ ) (table 2). The postoperative complication rate was almost similar between the groups: 271 of 433 patients (62.2%) in the OE group and 260 of 433 (60.2%) patients in the MIE group ( $p=0.468$ ) had one or more complications. Mortality was not statistically significant different between the groups: 3.0% (OE) versus 4.7% (MIE) ( $p=0.209$ ). Anastomotic leakage (15.5% vs. 21.2 %,  $p=0.028$ ), reinterventions (21.1% vs. 28.8%,  $p=0.017$ ) and gastric conduit necrosis (0.2% vs. 3.2 %,  $p=0.001$ ) were more frequently observed in the MIE group. Detailed information on the severity and treatment of anastomotic leakages is shown in table 2b. Subgroup analyses showed that an anastomotic leak after MIE was more frequently seen after an Ivor Lewis esophagectomy (21% (MIE) vs. 10% (OE),  $p=0.010$ ) compared to the McKeown group (23% (MIE) vs. 17% (OE),  $p=0.056$ ).

There was a statistically significant shorter hospital stay in the MIE group (13 vs. 14 days,  $p=0.001$ ). The readmission rate was similar for patients after OE compared to MIE: 12.5% versus 12.9%, respectively;  $p=0.704$ )

**Table 2a.** Peri operative outcomes

Outcomes		Before Matching					After Matching				
		OE (N =500)		MIE(N=1227)		<i>p</i> value	OE (N=433)		MIE(N=433)		<i>p</i> value
		n		n			n		n		
<b>Conversion rate</b>		n.a.	n.a.	35	2.8%	n.a.	n.a.	n.a.	14	3.4%	n.a.
<b>Postoperative complications</b>	Total	316	63.2%	735	59.9%	0.203	271	62.2%	260	60.2%	0.468
	Grade 1	161	32.2%	300	24.4%	0.587	117	27.0%	97	22.4%	0.797
	Grade 2	52	10.4%	125	10.2%		64	14.8%	74	17.1%	
	Grade 3	6	1.2%	21	1.7%		6	1.4%	8	1.8%	
	Grade 4	20	4.0%	31	2.5%		13	3.0%	13	3.0%	
	Grade n.s.	77	15.4%	258	21.1%		71	16.4%	68	15.7%	
<b>Pulmonary complications</b>		182	36.4%	411	33.5%	0.249	148	34.2%	154	35.6%	0.669

Table 2a continued. Peri operative outcomes

		Before Matching					After Matching				
<b>Anastomotic leakage</b>		78	15.6%	260	21.2%	0.008	67	15,5%	92	21.2%	0.028
<b>Chylothorax</b>		43	8.6%	135	11.0%	0.136	38	8,8%	46	10.6%	0.358
<b>Cardiac complications</b>		71	14.2%	174	14.2%	0.992	56	12,9%	59	13.6%	0.764
<b>Postoperative bleeding</b>		8	1.6%	14	1.1%	0.440	8	1,8%	7	1.6%	0.795
<b>Fascial dehiscence</b>		5	1.0%	4	0.3%	0.078	3	0,7%	2	0.5%	0.654
<b>Gastric conduit necrosis</b>		2	0.4%	29	2.4%	0.005	1	0,2%	14	3.2%	0.001
<b>Recurrent laryngeal nerve injury</b>		21	4.2%	53	4.3%	0.911	17	3,9%	25	5.8%	0.206
<b>Reintervention</b>	Total	99	19.8%	351	28.6%	<0.001	89	21,1%	119	28.2%	0.017
	Under GA	58	11.6%	210	17.1%	0.004	52	12.3%	76	18.0%	0.021
<b>30- d postoperative mortality</b>		20	4.0%	54	4.4%	0.719	13	3,0%	20	4.7%	0.209
<b>ICU stay (days)</b>		3	(0-155)	2	(0-125)	<0.001	3	(0-155)	2	(0-82)	0.418
<b>Hospital stay (days)</b>		15	(4-152)	12	(3-197)	<0.001	14	(4-156)	13	(4-200)	0.001
<b>Readmission</b>		60	12.0%	189	15.4%	0.067	54	12,5%	56	12.9%	0.704

**Legend.** Data are n (%), median (range) and mean ( $\pm$ SD).

**Abbreviations.** NA: not applicable, OE: open esophagectomy, MIE: minimally invasive esophagectomy, ICU: Intensive Care Unit. GA: General Anesthesia, NS: not specified. Severity postoperative complications: Grade 1: temporary disadvantage as a result of complication, but full recovery without reintervention Grade 2: complete recovery after reintervention Grade 3: complication caused permanent injury to the patient Grade 4: patient deceased at the consequences of complication

**Table 2b.** Anastomotic leakage: treatment

<b>Anastomotic leakage</b>										
<b>Characteristic</b>		<b>Total (N=159)</b>			<b>OE (N=67)</b>			<b>MIE (N=92)</b>		
		n	(N=159)	(N=866)	n	(N=67)	(N=433)	n	(N=92)	(N=433)
<b>Conservative treatment</b>		36	22.6%	4.2%	22	32.8%	5.1%	14	15.2%	3.2%
<b>Reinterventions</b>	Total	121	76.1%	14.0%	44	65.6%	10.1%	77	83.7%	17.8%
	Surgical	69	43.4%	8.0%	22	32.8%	5.1%	47	51.1%	10.9%
	Endoscopic	66	41.5%	7.6%	15	22.4%	3.5%	51	55.4%	11.8%
	NS	2	1.3%	0.2%	7	10.4%	1.5%	1	1.1%	0.2%
<b>Reintervention under GA</b>		70	44.0%	8.1%	22	32.8%	5.1%	48	52.2%	11.1%

**Legend.** Data are n (%), median (range) and mean ( $\pm$ SD), \* skewed distribution, Mann-Whitney test applied.

**Abbreviations.** NS: not specified, GA General Anesthesia. P values of differences between groups (OE and MIE) in patients who developed anastomotic leakage.

## Pathology

Pathological TNM stage was not significantly different between the groups (table 3). A resection with negative margins was achieved in 93,8% of patients after OE and in 93.1% of patients after MIE ( $p=0.390$ ). The median (range) number of resected lymph nodes was higher for the MIE group compared to the OE group: 20 (2-59) vs. 18 (0-53);  $p<0.001$ ).

**Table 3.** Histopathological outcomes

<b>Outcomes</b>	<b>Before Matching</b>					<b>After Matching</b>				
	<b>OE</b>		<b>MIE (N=1227)</b>			<b>OE</b>		<b>MIE</b>		
	<b>(N=500 )</b>					<b>(N=433)</b>		<b>(N=433)</b>		
	n		n		<i>p value</i>	n		n		<i>p value</i>
<b>Resection type</b>										
<b>R0</b>	465	93.0%	1154	94.1%	0.055	406	93.8%	403	93.1%	0.390
<b>R1/R2</b>	33	7.0%	53	4.3%		25	5.8%	25	5.8%	
<b>Unknown</b>	2	0.4%	20	1.6%		2	0.5%	2	0.5%	
<b>Lymph node yield</b>	18	(0-53)	21	(2-59)	< 0.001	18	(2-53)	20	(2-52)	0.001

**Table 3 continued.** Histopathological outcomes

	Before Matching					After Matching				
<b>pT stage</b>										
<b>Tis</b>	4	0.8%	6	0.4%	0.065	2	0.5%	3	0.7%	0.097
<b>T0</b>	115	23.0%	277	22.6%		106	25.1%	106	25.1%	
<b>T1</b>	63	12.6%	243	19.8%		56	13.3%	76	19.5%	
<b>T2</b>	105	21.0%	199	16.2%		84	19.9%	71	18.0%	
<b>T3</b>	193	38.6%	409	33.3%		168	39.8%	127	32.2%	
<b>T4</b>	4	0.8%	9	0.7%		3	0.7%	5	1.3%	
<b>Tx</b>	16	3.2%	84	6.8%		14	3.2%	45	10.4%	
<b>pNstage</b>										
<b>N0</b>	292	58.4%	705	57.5%	0.761	255	60.3%	235	59.6%	0.598
<b>N1</b>	117	23.4%	249	20.2%		101	23.9%	84	21.3%	
<b>N2</b>	55	11.0%	130	10.6%		48	11.3%	52	13.2%	
<b>N3</b>	24	4.8%	67	5.5%		18	4.3%	22	5.6%	
<b>Tx</b>	12	2.4%	76	6.2%		11	2.5%	40	9.2%	
<b>pMstage</b>										
<b>M0</b>	489	97.8%	1167	95.1%	0.732	424	97.9%	402	92.8%	0.743
<b>M1</b>	3	0.6%	9	0.8%		2	0.5%	5	1.2%	
<b>Mx</b>	8	1.6%	51	4.2%		7	1.6%	26	6.0%	

**Legend.** Data are n (%), median (range) and mean ( $\pm$ SD).

**Abbreviations.** OE = open esophagectomy, MIE = minimally invasive esophagectomy.

## Discussion

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The present study shows an increasing trend in the utilization of MIE in the Netherlands over the study period. In 2015, 84% of all transthoracic esophagectomies were performed using a minimally invasive approach, resulting in a higher lymph node yield and a similar R0 resection rate. There was no clinically relevant difference in mortality and pulmonary complications between OE and MIE, but anastomotic leaks, gastric conduit necrosis and reinterventions were more frequently observed in patients after MIE. Nevertheless, MIE was associated with a shorter hospital stay.

The percentage of patients operated via a minimally invasive approach is high compared to other national databases.<sup>17,18</sup> The studies from the USA and UK report that approximately 25% of the esophagectomies are performed via a minimally invasive approach. To obtain a homogeneous group of patients, hybrid procedures were excluded. Hybrid esophagectomy (laparoscopy with thoracotomy) is associated with a reduction in postoperative complications.<sup>17,18</sup> Hence, OE is only performed in 16% of patients in the Netherlands. This shows that in a rather small country with approximately 22 hospitals performing esophageal cancer surgery, the diffusion of minimally invasive techniques has taken place in a short time period, which was facilitated by several factors. Although the Netherlands have not got a formal proctor program for MIE, all upper gastrointestinal surgeons had at least basic minimally invasive skills and were performing open esophageal surgery before starting MIE. Most surgeons started MIE after participating in a hands-on course on minimally invasive gastrectomy and esophagectomy in the Netherlands, organized by the European Society of Surgical Oncology (ESSO). Secondly, most centers were proctored by a more experienced surgeon performing minimally invasive upper GI surgery for the first 3 to 10 procedures. Surgeons were able to adapt to new techniques and change their practice accordingly. However, given the findings of our study, this period might even have been too short.

Given that the vast majority of esophageal cancer resections are performed using a minimally invasive approach, it is of great importance to monitor outcomes on a nationwide level. The finding of an increased anastomotic leak- and reintervention rate after MIE needs a further in depth analysis since postoperative morbidity is associated with a decreased long-term survival and quality of life and increased costs.<sup>19-22</sup> Moreover, the anastomotic leak rate was

not only higher in the MIE group, but the leaks were also associated with a higher rate of surgical and endoscopic reinterventions and more reinterventions under general anesthesia. Gastric conduit necrosis was more frequently observed in the MIE group. This may be a manifestation of a major anastomotic leakage but may also be a result of problems maintaining an adequate blood supply so that the graft remains viable due to technical difficulties.

Mamidanna et al.<sup>23</sup> also found a higher reintervention rate after MIE in their population based study from the UK. However, they were not able to present detailed information on postoperative complications, since the authors collected the data from a retrospective, administrative database. Furthermore, the authors stated that their data did not entail the learning curve of introducing MIE although the proportion of MIE increased from 6,2 % to 24,7% during the study period. Mackenzie et al.<sup>24</sup> recently published a study on the national proficiency-gain curves for MIE. It was concluded that the introduction of MIE was associated with a proficiency-gain curve for mortality and major morbidity.<sup>25</sup> This effect may at least partially explain the results of Mamidanna et al.<sup>23</sup> since the study population was largely overlapping.

Another population-based study from the USA<sup>26</sup> also found that OE and MIE are equivalent in terms of overall morbidity and mortality. However, MIE was associated with a higher reintervention rate during its introduction. The authors stated that this was possibly reflecting a learning curve. Since data on the exact numbers of MIE performed in each hospital before 2011 are lacking and the hospital in which patients had surgery is kept anonymous due to privacy regulations in the current study, we cannot deduct from our data whether there is a causal relationship between a proficiency-gain curve for morbidity and the increased incidence of anastomotic leakage and reinterventions after MIE. Nevertheless, this may be the case in our series as MIE was introduced in most centers during the study period. In particular, anastomotic leakage (which was increased after MIE) is correlated with an incompleting learning curve.<sup>24</sup>

Our subgroup analyses showed that the anastomotic leak rate after MIE was higher after an Ivor Lewis procedure compared to a McKeown procedure. This supports our hypothesis that the increased anastomotic leak rate after MIE might be due to a learning curve, since

the anastomotic technique in the McKeown procedure is likely to be similar for the OE and MIE group.

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MIE has shown to be feasible and safe in various single- and multi center cohort studies. These studies report data from high volume centers by surgeons who had already passed their learning curve.<sup>10, 11, 12</sup> In the only randomized controlled trial published in full text to date (TIME trial), MIE resulted in a lower pulmonary complication rate, shorter hospital stay and a better short-term quality of life than OE.<sup>12</sup> The shorter hospital stay is also shown by the current data, however the reduced perioperative pulmonary morbidity could not be demonstrated. As discussed above, this also might be a result of a proficiency-gain curve. At the same time it is questionable if the present study and the TIME trial can be compared. In the present study, pulmonary complications were defined as clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome (ARDS). The TIME trial only included data on pneumonia and pulmonary embolism. Randomized studies and other retrospective studies may not always give a balanced view on OE or MIE given the stringent in- and exclusion criteria and because of several bias's inherent to retrospective cohort studies. Therefore, results might not always apply to the general population. This is well illustrated in the TIME trial. In view of the significant (inverse) relation between postoperative morbidity and hospital volume for esophagectomy, the participating hospitals had to perform more than 30 esophagectomies per year.<sup>27,28,29</sup>

During the study period of the current study, this target was reached by less than 50% of hospitals included in the current study.<sup>16</sup> This has initiated centralization of esophageal cancer surgery in the Netherlands. Since 2011, all centers performing esophagectomies in the Netherlands are obliged to perform at least 20 esophageal resections for cancer per year.<sup>30</sup> In 2011, only 9 of 20 (45%) hospitals performed more than 20 esophagectomies per year, whereas in 2014, 18 out of 22 (82%) hospitals met this criterion.<sup>16</sup> Further centralization of esophagectomies (minimum of 40-60 per year) may improve postoperative outcomes.<sup>31</sup>

Besides avoiding unnecessary patient harm by appropriate proctoring during the introduction of MIE and stimulating the process of centralization for esophageal cancer surgery, technical



aspects of MIE including lymph node dissection, location of the anastomosis as well as the best technique may have to be further optimized and attuned to the patient further improve the outcome of MIE.

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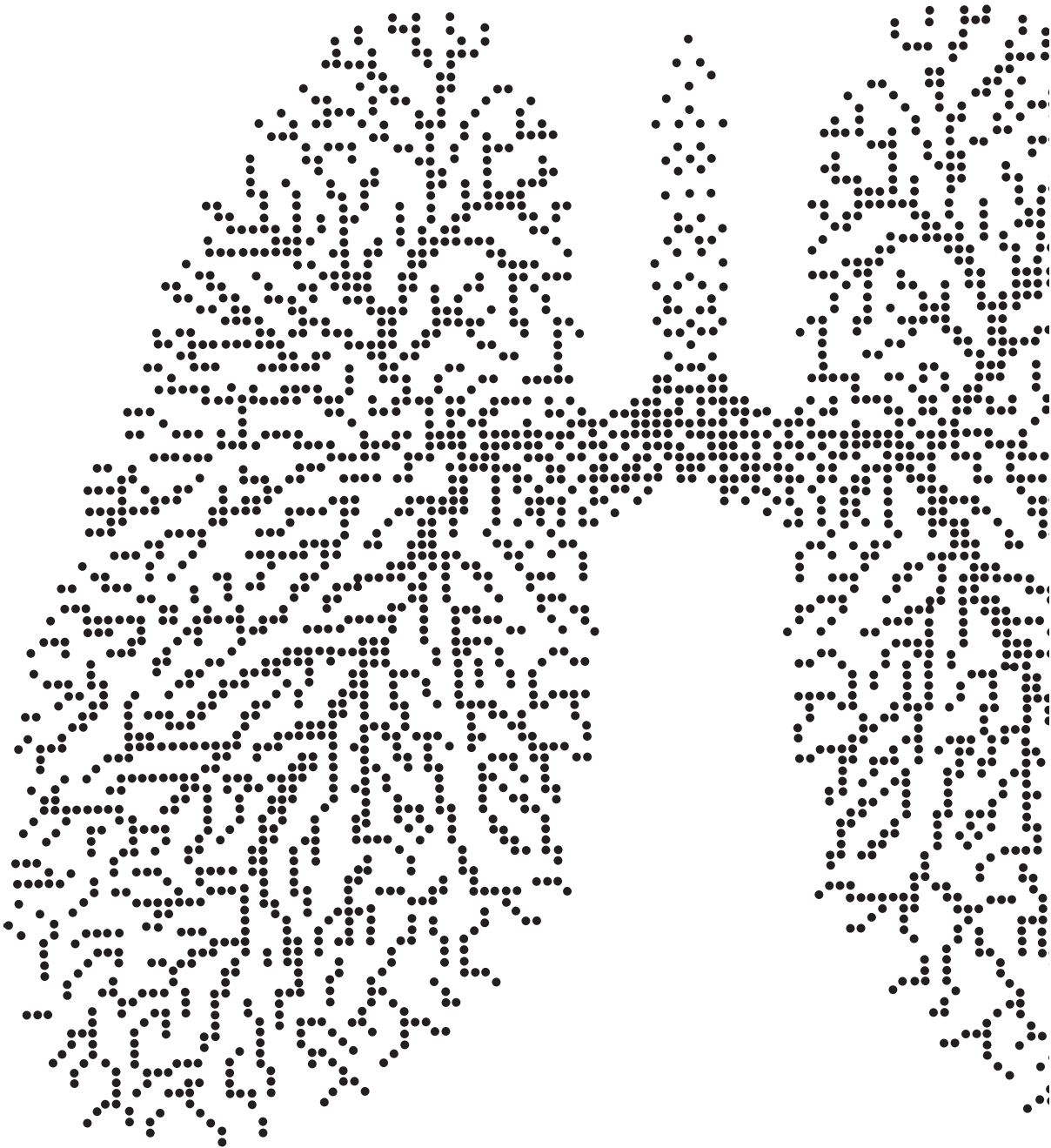
The strength of this study is the prospective, population-based data set with detailed information on postoperative complications. Despite this, certain limitations apply to the current analysis. It was not possible to obtain data on a proficiency-gain curve. Furthermore, despite correction for baseline characteristics through propensity score matching, the inability of propensity score matching to adjust for unknown confounders that may explain some of our findings remains a limitation.

Within the context of these limitations, the present study shows that MIE was associated with a shorter hospital stay. MIE was oncologically safe but did not reduce pulmonary complications and resulted in a higher anastomotic leakage- and reintervention rate, which warrants further analysis.

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# Chapter 4

## Robot Assisted Minimally Invasive Esophagectomy

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*Der Chirurg. 2017 Jan;88(Suppl 1):7*

## Abstract

Esophagolymphadenectomy is the corner stone of multimodality treatment for resectable esophageal cancer. The preferred surgical approach is transthoracic, with a two-field lymph node dissection and gastric conduit reconstruction. It has been shown that a minimally invasive approach may reduce postoperative complications and increase quality of life. Robot-assisted minimally invasive esophagectomy (RAMIE) was developed to facilitate this complex thoracoscopic procedure. RAMIE has been shown to be safe with good oncological results and reduced morbidity. The use of RAMIE opens new indications for curative surgery in patients with T4b tumors, high mediastinal tumors and lymph node metastases after neoadjuvant treatment.

## Background

Annually, 482.300 patients are diagnosed with esophageal cancer worldwide, and 406.800 patients die of this disease.<sup>1</sup> Esophagolymphadenectomy is the corner stone of multimodality treatment for locally advanced esophageal cancer.<sup>2-3</sup> The preferred curative treatment for esophageal cancer is a transthoracic esophagectomy with a two-field lymph node dissection and gastric conduit reconstruction.<sup>4</sup> This procedure allows for en bloc resection of the esophagus and extensive mediastinal lymphadenectomy.<sup>5</sup>

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Minimally invasive surgery was introduced to reduce surgical trauma and postoperative morbidity. Minimally invasive esophagectomy (MIE) has several advantages over open esophagectomy, such as diminished blood loss, reduced morbidity and shorter hospital stay<sup>6,7</sup> However, conventional thoracoscopic techniques are limited by a two-dimensional view, a disturbed eye-hand coordination and a reduced freedom of movement. These technical limitations may compromise the feasibility of MIE and its worldwide adaptation.<sup>8-10</sup>

In 2003, the robot-assisted thoraco-laparoscopic approach was developed at the University Medical Center Utrecht (UMC Utrecht), the Netherlands.<sup>10</sup> Robot-assisted minimally invasive esophagectomy (RAMIE) reduces the limitations of thoracoscopic esophagectomy by a stable 3D, 10 times enlarged image, restored eye-hand axis, and excellent dexterity with the endowristed instruments. In this article we present our technique, give suggestions for successful implementation, discuss recent developments and look to the future directions of RAMIE.

## RAMIE at UMC Utrecht

### Preparation

General and thoracic epidural anesthetics are combined to ensure sufficient intraoperative and postoperative analgesia. Recently we started using single-dose and bilateral paravertebral block combined with sufentanil in the context of our enhanced recovery after esophagectomy program. This may provide similar postoperative analgesia and early discharge avoiding the disadvantages of epidural anesthesia such as catheter malposition and hypotension.<sup>11</sup> The patient is intubated with a left-side double-lumen tube and is positioned in the left lateral decubitus position, tilted 45 degrees to the prone position. The robotic system (daVinci Si system, Intuitive Surgical Inc., Sunnyvale, CA, USA) is positioned on the dorsocranial side of the patient (figure 1). Three ports are placed for the robotic system as well as two ports for the assisting surgeon (figure 2), whereafter the right lung is desufflated. Through one of the assistant ports, CO<sub>2</sub> at 6 mmHg is insufflated to keep the lung out of the operative field.

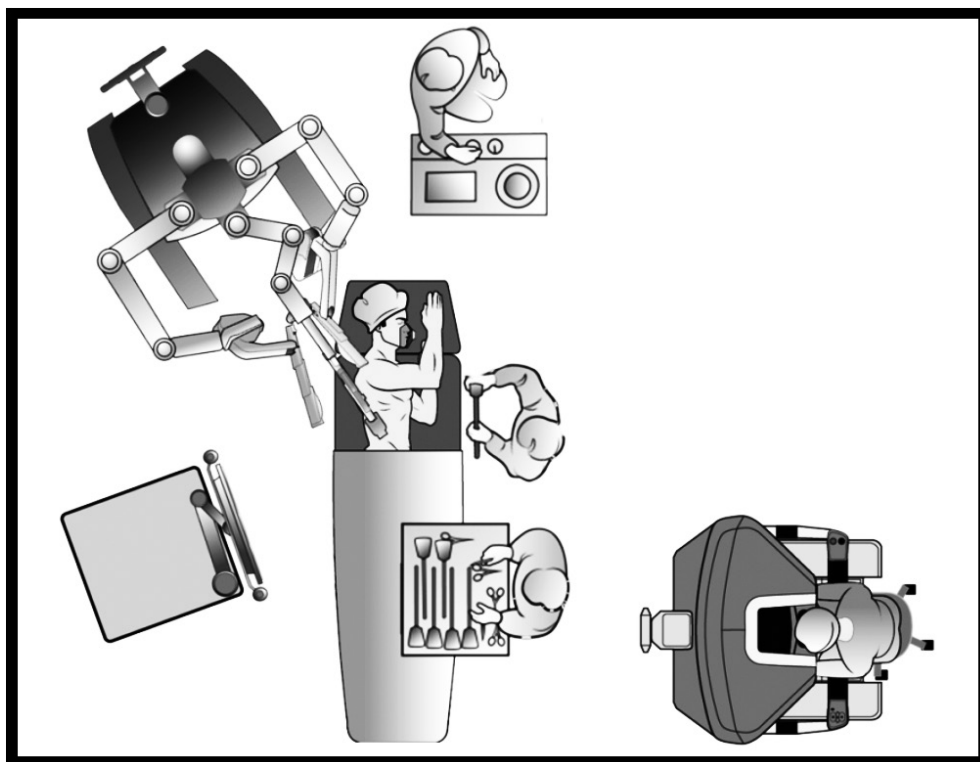
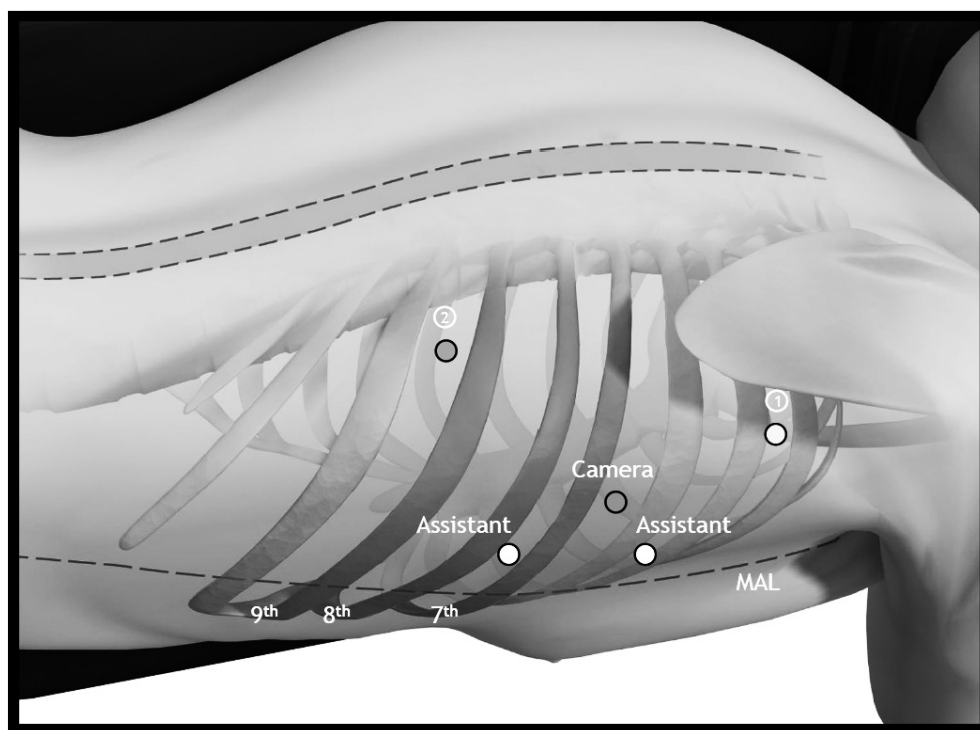


Figure 1. Operation room setup



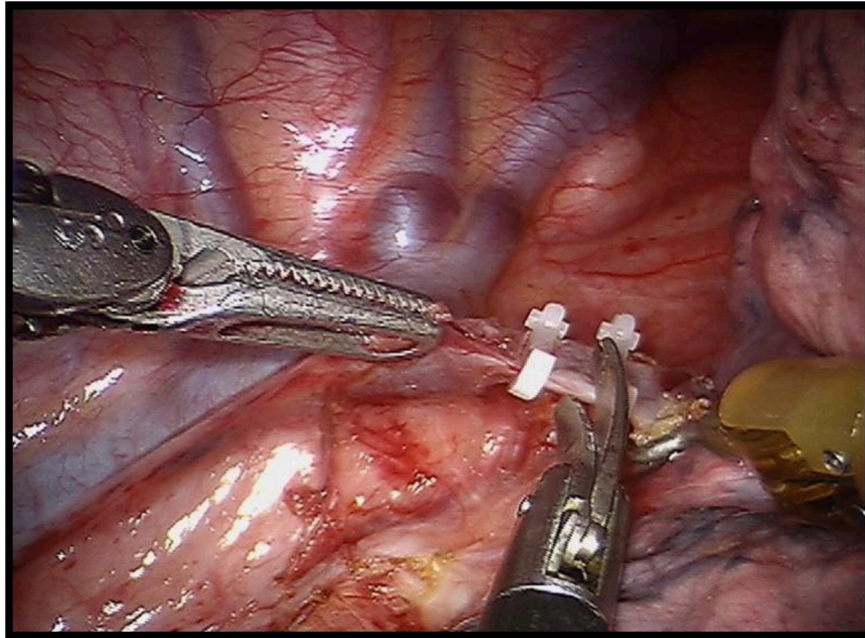
## Surgery

The right pulmonary ligament is divided and the parietal pleura is dissected at the anterior side of the esophagus from the diaphragm up to the level of the azygos arch. The azygos arch is ligated with robotic Hem-o-lok clips. (Teleflex Medical, Weck Driv. NC, USA) and divided. These clips are endowristed facilitating precise positioning (Figure 3). To establish dissection of the right paratracheal lymph nodes, dissection of the parietal pleura is continued above the azygos arch. The right vagal nerve is dissected below the level of the carina to preserve its pulmonary branches.<sup>12,13</sup> Dissection of the parietal pleura is continued from cranially to caudally along the azygos vein at the posterior side of the esophagus.



**Figure 2.** Trocar placement in the thoracic phase.

**Legend:** Robotic arms: 1 (yellow), 2 (green) and camera (blue). Two assisting ports (white)



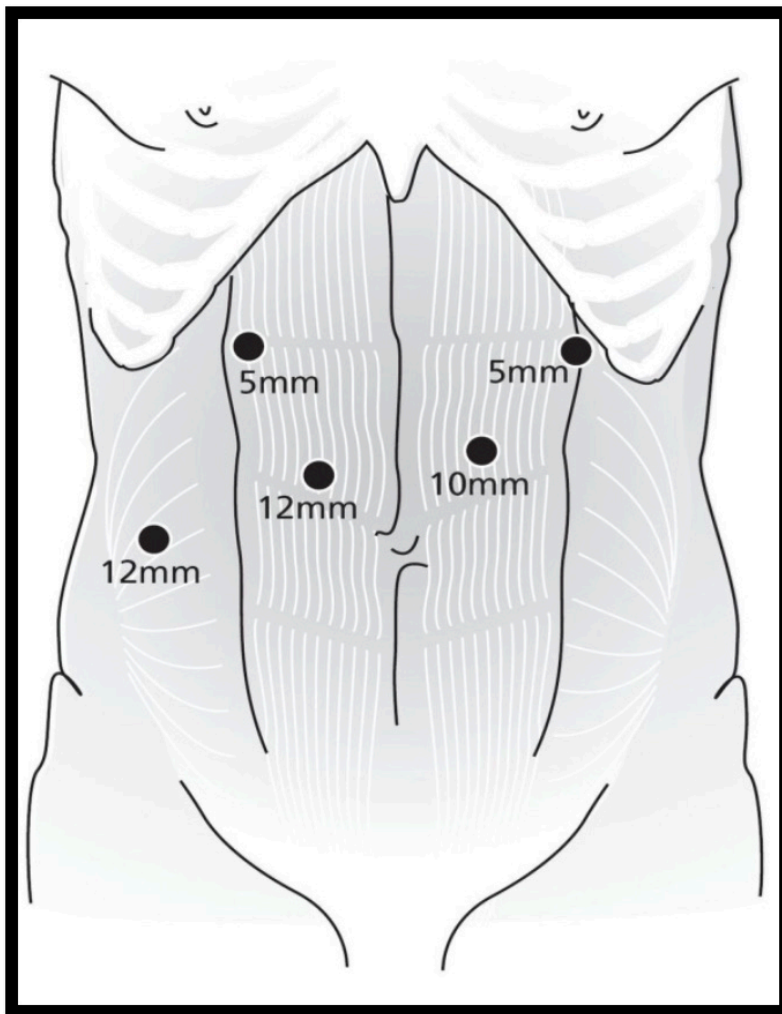
**Figure 3.** Clipping and dissection of the azygos vein

Paratracheally left, the left recurrent nerve is identified and carefully protected. At the level of the diaphragm, the thoracic duct is clipped with the robotic Hem-o-lok clips to prevent leakage. At this level, a Penrose drain is placed around the esophagus to facilitate traction and esophageal mobilization. The esophagus is then resected from the diaphragm up to the thoracic inlet en bloc with the surrounding mediastinal and subcarinal lymph nodes and the thoracic duct. Aortoesophageal arteries are identified and clipped.

The patient is put in supine position for the abdominal phase. After introduction of the 5 trocars (figure 4) the hepatogastric ligament is opened and transection of the lesser omentum is continued until the left crus of the diaphragm. Hereafter, the greater gastric curvature is dissected using a harmonic ace (Ethicon, Cincinnati, Ohio). An abdominal lymphadenectomy is performed including lymph nodes surrounding the celiac trunk, along the left gastric, and splenic artery and the lesser omental lymph nodes. The left gastric artery is ligated with Hem-o-lok (Teleflex Medical, Weck Driv, NC) and transected at its origin. Through a left-sided

vertical incision along the sternocleidomastoid muscle, the cervical phase of esophagectomy is initiated to facilitate mobilization of the cervical esophagus. No formal cervical lymph node dissection is carried out. The cervical esophagus is transected and a cord is attached to the specimen. The dissected esophagus with *en-bloc* the surrounding lymph nodes are pulled down through the mediastinum under laparoscopic view. Hereafter, the left para-umbilical

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**Figure 4.** Trocar placement in the abdominal phase

The resection specimen is removed through this incision with a wound drape (3M, St. Paul, Minnesota) to create the gastric conduit extracorporally. A linear stapler (GIATM 80, 3\_8mm; Medtronic, Minneapolis, Minnesota) is used to create a gastric conduit 4 cm wide, which is routinely oversewn with a 3/0 polydioxanone single-layer running suture. The gastric conduit is pulled up through the mediastinum along the original anatomic tract of the esophagus with the aid of a plastic tube (laparoscopic camera bag). A cervical handsewn end-to-side anastomosis is created between the gastric tube and the cervical esophagus using a 3/0 polydioxanone single-layer running suture. A feeding jejunostomy is placed in the second loop after the ligament of Treitz for postoperative feeding. The abdomen is closed in layers with PDS loop for the fascia and skin intracutaneously with monocryl.

### **Pushing the limits of esophagectomy with RAMIE**

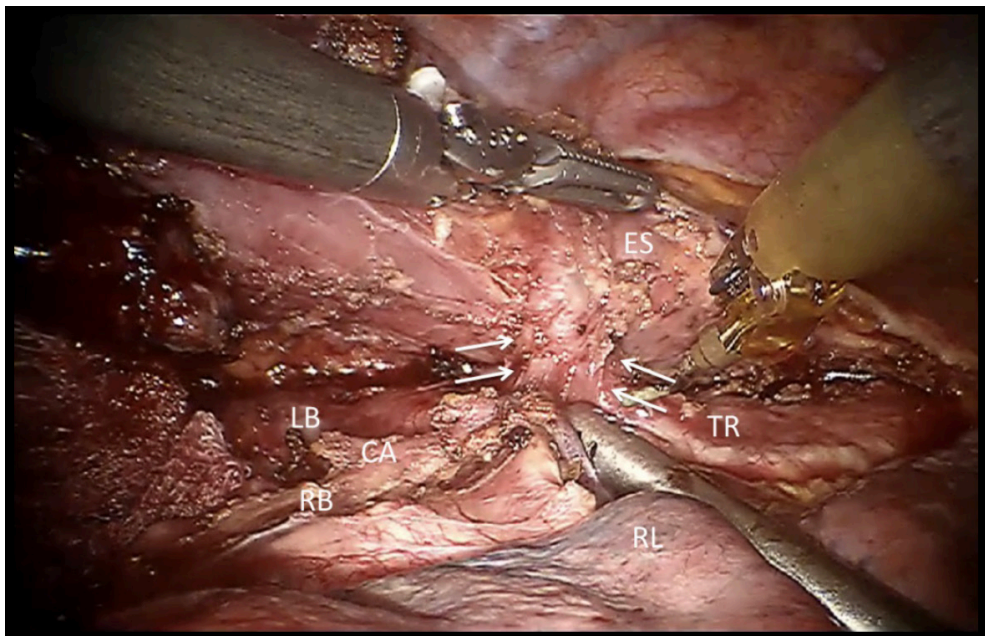
Since the introduction of RAMIE we have gained considerable experience with the use of the da Vinci robot in over 300 cases. After a learning curve of 120 cases a plateau was reached with a steady level of performance. Utilizing the full capabilities of the da Vinci robot we currently investigate new indications in patients previously inoperable with conventional surgery.

Until recently, patients with cT4b tumors were considered inoperable and guidelines recommend definitive chemoradiotherapy (dCRT) as the treatment of choice.<sup>14</sup> However, cT4 status is a negative predictor for locoregional control.<sup>15</sup> Definitive chemoradiotherapy is associated with a high rate of esophageal stenosis and perforation, the latter occurring in 25% of patients and most often these perforations are lethal. Furthermore functional results are poor and recurrence occurs frequently in up to 41%.<sup>15, 16</sup> Therefore, we started salvage surgery with RAMIE in patients with cT4b esophageal tumors after long-course chemoradiotherapy. The patients are restaged with PET-CT and endobronchial ultrasound to determine the actual situation and selected for salvage surgery if tracheal ingrowth has been reduced (figure 5). The very precise dissection and enlarged 3D image allows for very precise dissection of the irradiated tumor tissue from the trachea, bronchi and aorta. The level of precision makes dissection in downstaged T4b tumors feasible. So far, we have treated 10 patients with this strategy leading to radical resections in 90% (unpublished data). The long-term oncologic and functional results are to be awaited before such an approach can be recommended for all patients.

Also, the upper mediastinum and thoracic aperture can be reached with excellent 3D view and magnified observation of the operative field (figure 6)(17). In this way, we were able to achieve a R0 resection in 28 out of 29 (97%) patients with upper esophageal tumors and paratracheal lymph nodes (unpublished data).

Future directions include the use of the robotic platform for image guided surgery and fluorescence detection of lymph nodes and tumor margins. The integration of optical imaging modalities that specifically visualize the areas of interest may reduce complications and improve the surgical accuracy of lymph node dissection.<sup>18</sup>

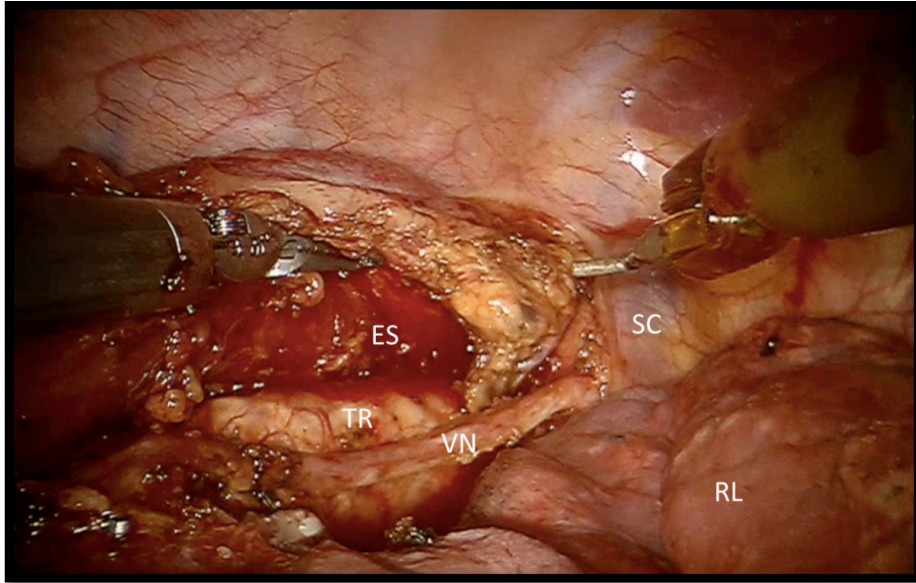
Another application of intravascular fluorescence dye imaging is the intraoperatively assessment of the vascularization of the gastric conduit. This may guide to the optimal site of the anastomosis and thereby contribute to reduce anastomotic leakage.<sup>19</sup>



**Figure 5.** T4b esophageal tumors, tracheal involvement.

**Legend.** ES: Esophagus, CA: Carina, LB: Left Bronchus, RB: Right Bronchus TR: Trachea, RL: Right Lung.





**Figure 6.** Upper mediastinum.

**Legend.** ES: Esophagus, VN: Vagal Nerve, TR: Trachea, RL: Right Lung, SC: Subclavian Artery.

### **Surgical Training Program**

We have developed a structured training program that enables esophageal surgeons to be guided through the learning curve in 20 cases. The proctored surgeons should have basic minimally invasive skills and knowledge of esophageal surgery. The program starts with 3 case observations in a RAMIE expert center, followed by a basic robotic course and a cadaveric lab. Thereafter, the proctor supervises the surgeon for the first 3-10 cases and reviews his skills after the first 20.

Optimal team performance during technically complex procedures requires a dedicated team (20). Therefore, at least 2 motivated surgeons, a dedicated anesthetist and a scrub nurse should be involved in the program. A sufficient case load (>20/year) and guaranteed access to a robotic system are of crucial importance.<sup>21,22</sup> In urology, proctoring has proven to be an essential mechanism for successful implementation of robot assisted radical prostatectomy and this approach is comparable in RAMIE.<sup>23</sup>

## Discussion

Ramie offers a 3D, magnified surgical view combined with a high degree of freedom of the articulating instruments. This facilitates meticulous dissection from diaphragm to thoracic inlet. Especially for the thoracic phase, where the esophagus is surrounded by delicate vital structures such as trachea, pulmonary veins, aorta and recurrent nerves, these features are of great value. These features allow the exploration of salvage surgery in patients with previously inoperable T4b and upper mediastinal tumors.

Robotic assistance may also facilitate the use of an intrathoracic anastomosis.<sup>24</sup> Until recently we performed a three stage esophagectomy (McKeown procedure) with a hand-sewn esophagogastric anastomosis in the left side of the neck as stated above. However, the incidence of anastomotic leakage after cervical esophagogastronomy remains relatively high (10-30%) and intrathoracic manifestation occurs in more than half of patients with cervical anastomotic leakage.<sup>25,26</sup> The incidence of leakage from intrathoracic anastomosis is reported to be lower.<sup>27</sup> Therefore, we started performing a two stage (Ivor-Lewis) procedure with a robotic hand-sewn intrathoracic anastomosis for distal esophageal tumors. Constructing an intrathoracic anastomosis during conventional thoracoscopy is technically challenging. By working in the upper thoracic aperture, the instruments have to reach deep into the thorax, imposing problems in manipulation, through the fulcrum effect at the ribs.<sup>28</sup> The robot nullifies these problems due to the endo-wristed intracorporeal instruments, tremor filtering and its three-dimensional view of the surgical field. Therefore, in our opinion the robot contributes to a high quality intrathoracic anastomosis. The hand sewn robotic technique is very controlled and reliable in our first experience. Langer numbers of patients have to be treated with this technique to show the percentages of success rates and long term results.

So far we chose to perform the abdominal aspect of our procedure via a laparoscopic approach, since the da Vinci Si Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) was not constructed to facilitate multi-quadrant surgery. The new da Vinci Xi Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) has its four arms mounted on an overhead boom enabling multi-quadrant surgery without the need to redock the system. Results of the robotic abdominal phase are awaited in the near future.

In conclusion, robotic assisted minimally invasive esophagectomy with two-field lymphadenectomy is an excellent minimally invasive technique to dissect the esophagus from the mediastinum with radical lymphadenectomy. Additionally, it may provide new curative options in patients previously inoperable with conventional surgery.

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Robotic assistance reduces the limitations of MIE while retaining its advantages over open esophagectomy. Therefore, we initiated a randomized controlled trial, comparing robot-assisted and open three-phase esophagectomy to express the additional value of RAMIE over open esophagectomy in a true measure.<sup>29</sup> Short-term results are expected in 2016.

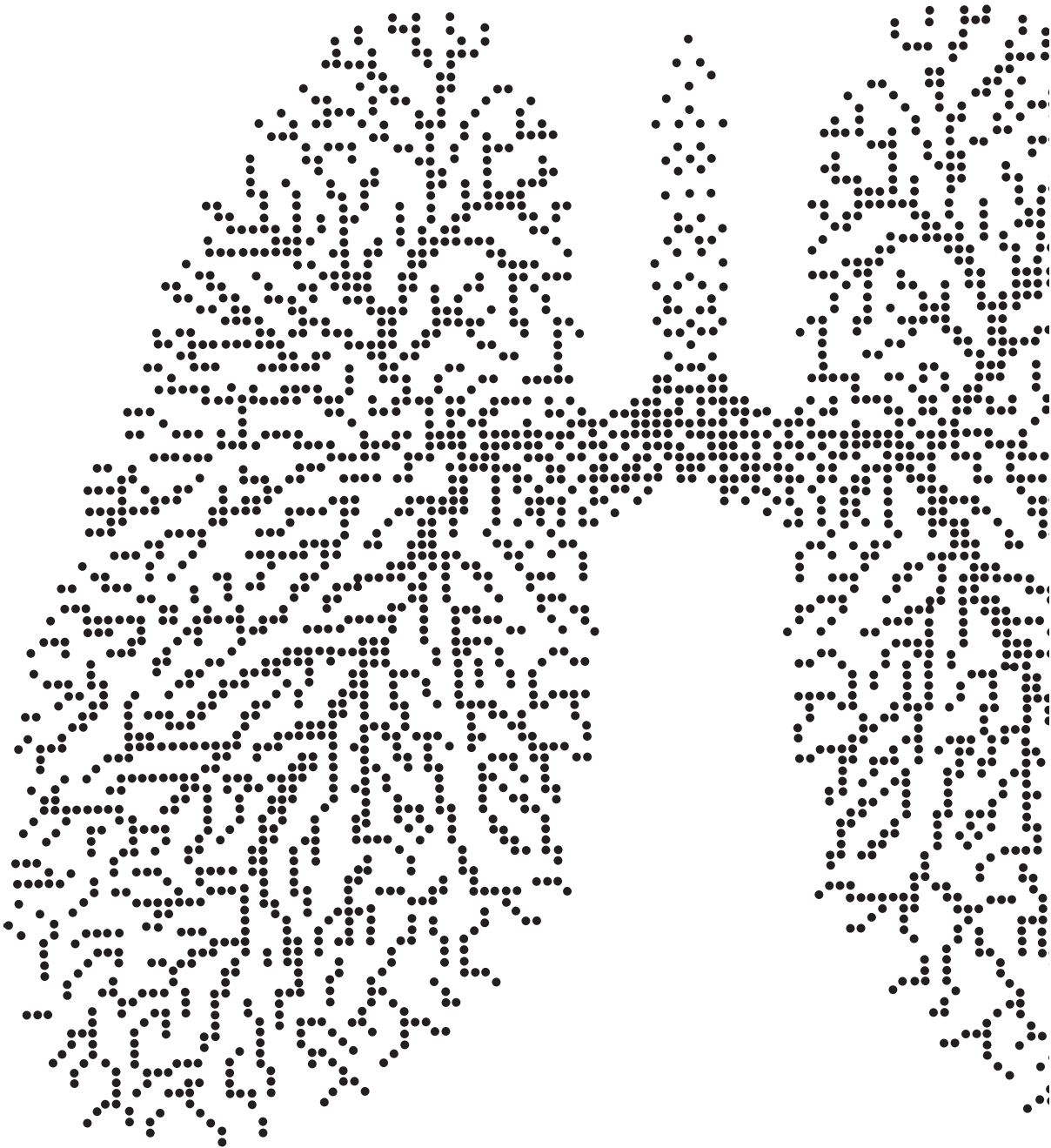


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# Chapter 5

## Minimally invasive esophagectomy: a propensity score matched analysis of semiprone versus prone position

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## Abstract

**Background:** The preferred surgical approach for esophageal cancer is a minimally invasive transthoracic esophagectomy with a two-field lymph node dissection. The thoracoscopic phase may be performed either in prone- or in left lateral decubitus position. Prone positioning has been associated with better pulmonary outcomes compared to left lateral decubitus positioning, however conversion to a classic thoracotomy is more difficult. The semiprone position has been proposed as an alternative approach.

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**Materials & Methods:** A retrospective review of a prospectively maintained database (2008 - 2014) was performed to compare postoperative complications, surgical radicality and lymph node yield between patients who underwent three-stage minimally invasive transthoracic esophagectomy in either the prone or semiprone position. Comparative analyses were conducted before and after propensity score matching.

**Results:** A total of 121 patients were included. In total 82 patients underwent minimally invasive esophagectomy in semiprone position and 39 patients in prone position. After propensity score matching both groups consisted of 39 patients. The operative time in the semiprone group was longer (368 vs. 225 minutes,  $P<0.001$ ) and in this group the lymph node yield was significantly higher (16 (range 6-80) vs. 13 (range 3-33),  $P=0.019$ ). There were no statistically significant differences regarding radical resections, postoperative complications and hospital stay.

**Conclusion:** The use of semiprone positioning in minimally invasive esophagectomy is safe, feasible and at least comparable to minimally invasive esophagectomy in prone position in terms of oncological clearance and postoperative complications.

## Background

Curative treatment for locoregional tumors of the esophagus or gastroesophageal junction consists of neoadjuvant chemo(radio)therapy followed by surgical resection with radical lymphadenectomy.<sup>1</sup> Minimally invasive esophagectomy (MIE) has been shown to reduce the trauma of surgery compared to an open (transthoracic) approach, resulting in a decreased morbidity and mortality after learning curve completion.<sup>2-4</sup> As a consequence, this procedure gained popularity in the last decade, especially in high volume centers.<sup>5</sup> The first thoracoscopic esophagectomy was performed in 1992 with the patient in left lateral decubitus (LLD) position.<sup>6</sup> To improve the exposure of the posterior mediastinum and obtain better ergonomic results, some authors suggested changing LLD to a prone position, introduced in 1994.<sup>7</sup> Currently, some retrospective studies suggest that MIE in prone position results in a reduction of pulmonary complications, blood loss, and an increase in mediastinal lymph node yield compared to MIE in LLD position.<sup>2</sup> Furthermore, MIE in prone position is suggested to decrease workload and provide for better ergonomic results.<sup>8</sup> On the other hand, conversion to a classic thoracotomy is probably more difficult in the prone position and special equipment and training is necessary to put the patient in prone position. The use of a modified semiprone position might overcome this problem while retaining the benefits of the prone position.<sup>4</sup> Therefore, this study aimed to compare 3 stage thoracoscopic esophagectomy in the prone position to the semiprone position with regard to postoperative complications and oncological clearance.

## Materials & Methods

### Patients

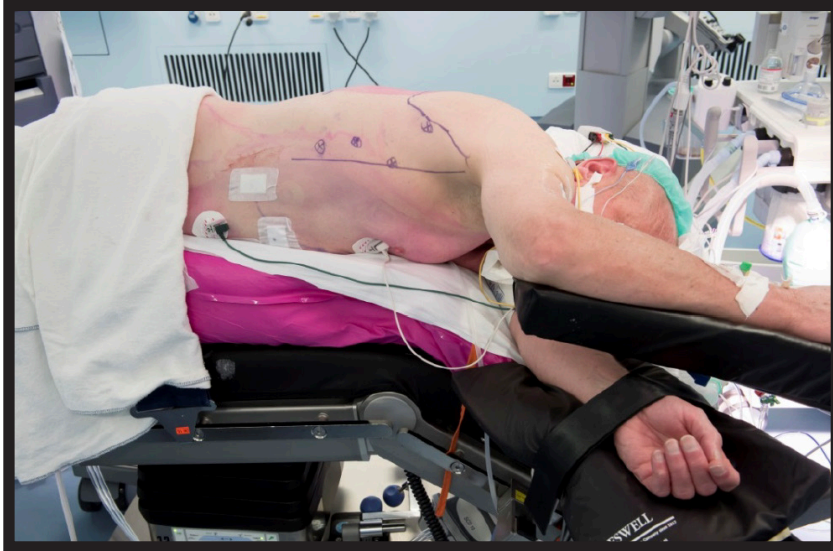
A retrospective review of a prospectively maintained database was performed to compare postoperative complications, surgical radicality and lymph node yield between patients who underwent MIE in prone and semiprone position. To create a homogeneous cohort all consecutive patients who underwent a three-stage minimally invasive esophagectomy with a two field lymphadenectomy, gastric conduit reconstruction and a left cervical anastomosis, either with or without neoadjuvant chemoradiotherapy. Between April 2008 and January 2014 in the Catharina Hospital Eindhoven and the University Medical Center Utrecht were included. All procedures were performed by dedicated upper gastrointestinal oncologic surgeons who had extensive experience in MIE in either prone or semiprone position. Patients whom underwent an emergency esophagectomy were excluded. Institutional Review Board approval for both centers was obtained, and informed consent requirement was waived for this study.

### Anesthesia

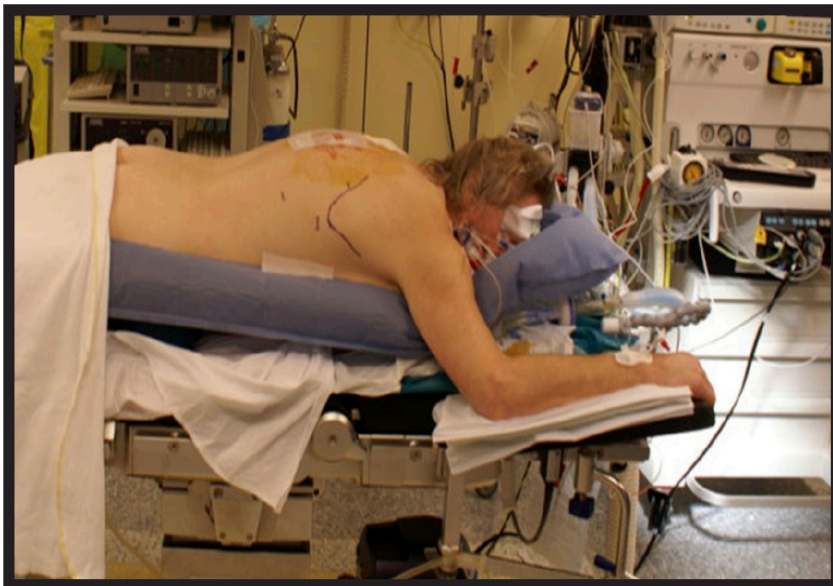
In order to provide adequate analgesia all patients received an epidural catheter (intercostal space T5-6, T6-7 or T7-T8) prior to surgery. Following prophylactic antibiotics (cefazolin 2.000 mg, metronidazole 500 mg), general anesthesia (intravenous propofol, sufentanil, and a muscle relaxant) were administered. In the semiprone group, endotracheal intubated was accomplished with a left-side double-lumen tube to enable desufflation of the right lung during the thoracic phase of the procedure. Subsequently, the patient was positioned in LLD position, tilted 45° to the prone position (figure 1A). A pressure-controlled ventilation strategy with a maximum pressure of 27 cm H<sub>2</sub>O and maximum tidal volume of 6 mL/kg was used during single-lung ventilation. To maintain end-tidal CO<sub>2</sub> between 40 and 45 mm/Hg tidal volumes were set at 6–8 mL/kg during double-lung ventilation. In the prone group, patients were placed in the swimmers position after intubation with a single-lumen endotracheal tube according the conventional procedure (figure 2A).

In this group, during the thoracic phase, double lung ventilation was maintained and an optimal view was established with 8 mmHg insufflational pressure. Tidal volumes were set between 3-5 ml/kg and ventilatory frequency between 18 and 28 per minute.





**Figure 1A.** Patient positioned in semiprone position.



**Figure 2A.** Patient positioned in prone position.

## **Surgery**

A 3 stage esophagectomy was performed with cervical anastomosis (McKeown procedure). Transthoracic mobilization of the esophagus and mediastinal lymph nodes dissection was performed in either semiprone or prone position (see description below). Subsequently, the patient was placed in supine position for conventional laparoscopic mobilization of the stomach, truncal lymph node dissection and an extracorporeal gastric conduit formation. Finally, a left cervical esophagogastric anastomosis was created through a left vertical neck incision along the anterior border of the sternocleidomastoid muscle.

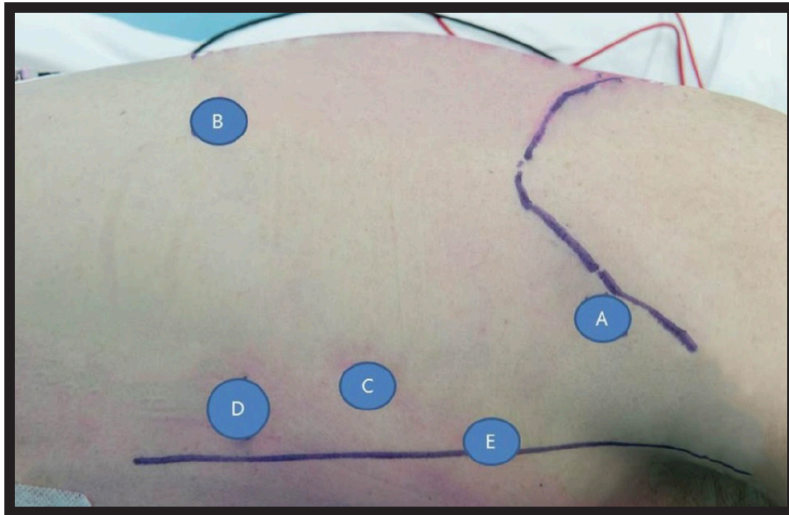
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### **Semiprone**

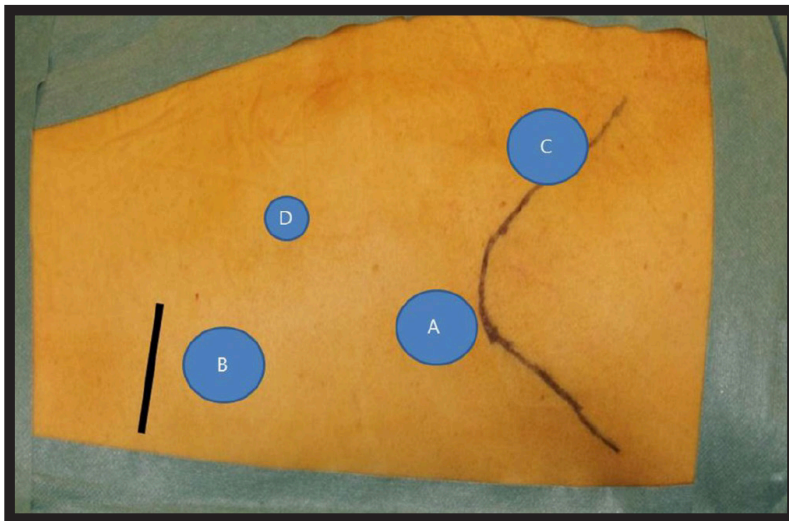
Three ports were placed for the robotic system, as well as two ports for the assisting surgeon (Figure 1B). After desufflating the right lung, CO<sub>2</sub> at 6 mmHg was insufflated through one of the assistant ports to keep the lung out of the operative field. Following division of the right pulmonary ligament, an extensive mediastinal lymph node dissection was performed (para-esophageal, infracarinal, aortic pulmonary window, subcarinal, paratracheal). The azygos arch was ligated and the thoracic duct was clipped at the level of the diaphragm. Hereafter, the esophagus was mobilized and resected en bloc with the surrounding mediastinal and subcarinal lymph nodes, and the thoracic duct. This technique has been described more thoroughly in previous studies.<sup>9-11</sup>

### **Prone**

A 12-mm camera port was placed posterior to the tip of the scapula and CO<sub>2</sub> insufflation was accomplished with a pressure of 8 mmHg. A second and third 12-mm port were placed in the 8th intercostal space in the right posterior axillary line and medial of the scapula respectively. A 5-mm port was placed halfway between the spine and the original 8th intercostal port (Figure 2B). By means of conventional thoracoscopy the mediastinal pleura was opened with a harmonic scalpel with subsequent mobilization of the esophagus. A mediastinal lymph node dissection was performed (para-esophageal, infracarinal, aortic pulmonary window, subcarinal).



**Figure 1B.** Trocar placement in the semiprone position. Robotic arms 1 (A) and 2 (B) camera (C), and two assisting ports (5mm) (D & E).



**Figure 2B.** Trocar placement in the prone position. A camera port (A), two 12-mm ports (B & C), and a 5-mm port (D)

A paratracheal lymph node dissection was not routinely performed and only on indication when lymph node metastases were suspected on preoperative staging. The Azygos vein was clipped with a hemolock® and transected. The main bronchi, trachea and pleura were dissected towards cranial. Hereafter the pleura was dissected towards the diaphragm where the thoracic duct was clipped. The mobilized esophagus was resected en bloc with the mediastinal lymph nodes.

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### **Postoperative care**

After surgery patients were admitted to the intensive care unit (ICU), while maintaining mechanical ventilation. Extubation was performed when patients were considered cardio-respiratory stable. Epidural analgesia was maintained during the first postoperative day. In addition, all patients were provided with patient-controlled opioid analgesia.

### **Outcomes**

The primary outcome was pneumonia, which was defined according to the criteria of the Uniform Pneumonia Score.<sup>12</sup> Secondary outcomes included intra-operative variables, such as total blood loss, length of operation and conversion rate. Furthermore, the number of harvested lymph nodes, radicality, in-hospital mortality, pulmonary embolism, clinically or radiologically proven anastomotic leakage, mediastinitis, chylothorax, recurrent laryngeal nerve palsy, wound infection, cardiac complications and intensive care unit and hospital stay were also included as secondary outcome measures.

### **Statistical analysis**

Perioperative outcomes of patients who underwent MIE were compared between patients in the semiprone and prone position. Propensity score matching was performed to create comparable treatment groups (prone versus semiprone) with regard to measured confounders. First, a propensity score for each patient was computed by logistic regression using the position of the patient during surgery as the dependent variable and the variables marked in Table 1 as covariates. Equal study groups were created by one-to-one nearest-neighbor matching without replacement. Values were presented as mean  $\pm$  standard deviation (SD) or median (range). The demographic and clinical data of both surgical groups were compared

with a Chi-square test or a Mann-Whitney U test. Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (<http://www.R-project.org>; 'MatchIt' and 'optmatch' packages). A *p*-value of <0.05 was considered statistically significant.

**Table 1.** Patient and treatment-related characteristics in relation to surgical procedure

		Before Matching					After Matching				
Characteristic		Semiprone (n=82)		Prone (n=39)		<i>p</i> value	Semiprone (n=39)		Prone (n=39)		<i>p</i> value
		n		n			n		n		
<b>Gender</b>	Female	31	37.8%	10	26%	0.649	13	33%	10	26%	0.456
	Male	51	62.2%	29	74%		26	67%	29	74%	
<b>Age (years)*</b>		62	±8.68	63	±8.93	0.186	63	±25.33	63	±8.93	0.492
<b>BMI (kg/m2)*</b>		24.95	±4.36	24.55	±4.5	0.515	25.34	±4.86	24.55	±4.5	0.478
<b>ASA score</b>	I	22	27%	1	2%	0.004	6	15%	1	2%	0.140
	II	49	60%	28	72%		24	62%	28	72%	
	III	11	13%	10	26%		9	23%	10	26%	
<b>COPD</b>	No	69	84.1%	35	90%	0.408	33	85%	35	90%	0.498
	Yes	13	15.9%	4	10%		6	15%	4	10%	
<b>Cardiac comorbidity</b>	No	61	74.4%	34	87%	0.109	34	87%	34	87%	1.000
	Yes	21	25.6%	5	13%		5	13%	5	13%	
<b>Diabetes mellitus</b>	No	75	91.5%	35	90%	0.758	37	95%	35	90%	0.395
	Yes	7	8.5%	4	10%		2	5%	4	10%	
<b>Smoking</b>	No	29	35.4%	23	59%	<0.001	19	49%	23	59%	0.364
	Yes	53	64.6%	16	41%		20	51%	16	41%	
<b>Alcohol</b>	No	25	30.5%	17	44%	0.174	13	33%	17	44%	0.532
	Yes	53	64.6%	22	46%		26	67%	22	46%	
<b>cT stage</b>	T1,2	24	29%	8	21%	0.307	10	26%	8	21%	0.591
	T3,4	58	71%	31	79%		29	74%	31	79%	
<b>cN stage</b>	N0	26	32%	8	21%	0.200	10	26%	8	21%	0.591
	N+	56	58%	31	79%		29	74%	31	79%	
<b>Histology</b>	ADC	43	53%	21	54%	0.938	23	59%	21	54%	0.648
	SCC	39	47%	18	46%		16	41%	18	46%	

**Table 1 continued.** Patient and treatment-related characteristics in relation to surgical procedure

		Before Matching					After Matching				
<b>Tumor location</b>	Proximal	6	7%	0	0%	0.093	2	5%	0	0%	0.108
	Middle	22	27%	16	41%		9	23%	16	41%	
	Distal	54	66%	23	59%		28	72%	23	59%	
<b>nCRT</b>	No	30	36.6%	3	8%	0.001	7	20%	3	8%	0.176
	Yes	52	63.4%	36	92%		32	80%	36	92%	

**Legend.** Data are expressed as N (%) or mean  $\pm$ SD.

**Abbreviations:** BMI = Body Mass Index, ASA = American Society of Anesthesiologists, COPD = Chronic Obstructive Pulmonary Disease, c = clinical, nCRT = neoadjuvant chemoradiotherapy. ADC = adenocarcinoma, SCC = squamous cell carcinoma. Neoadjuvant chemoradiotherapy consisted of intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m<sup>2</sup> of body-surface area] for 23 days) with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week).

## Results

A total of 121 patients were included. In 82 patients MIE was performed in semiprone position and in 39 patients in prone position. After propensity score matching both groups consisted of 39 patients. The clinical characteristics of the patients including propensity-matched groups are listed in Table 1. Patients in the prone group had a significantly higher ASA score, a smaller percentage of smokers and a higher number of patients that received neoadjuvant chemoradiotherapy. All of these variables did not show statistically significant differences between the two groups after propensity score matching. Table 2 demonstrates the intraoperative outcome of the patients. There was no statistically significant difference in pneumonia rate in semiprone position (49%) versus prone position (36%),  $P=0.252$ . The operative time in the semiprone group was longer (368 vs 225 minutes,  $P<0.001$ ) and in this group the lymph node yield was significantly higher (16 (range 6-80) vs. 13 (range 3-33),  $P=0.019$ ). However, when all paratracheally harvested lymph nodes were excluded from analysis this statistically significant difference ceases to exist (16 (range 2-78) vs. 13 (3-33),  $P=0.128$ ). There were no statistically significant differences between the semiprone and prone group in terms of blood loss (388 ml versus 300ml,  $P=0.753$ ), radical resections (both 92%,  $P=0.946$ ) and conversion rates (5% versus 10%,  $P=0.395$  (total number of conversions) and 5% versus 3%,  $P=0.556$  (conversions during thoracic phase)). The incidence of in-hospital mortality (3% versus 5%,  $P=0.314$ ), anastomotic leakage (26% versus 36%,  $P=0.326$ ), mediastinitis (13% versus 15%,  $P=0.745$ ) Chylothorax (38% vs 28%,  $P=0.337$ ), recurrent laryngeal nerve palsy (10% vs 8%  $P=0.692$ ), wound infection (15% versus 26%,  $P=0.644$ ), cardiac complications (15% versus 26%,  $P=0.262$ ) and the length of intensive care unit (1 day (range:1-16) versus 1 day (range 1-30),  $P=0.732$ ) and total hospital stay (18 days (range: 8-87) versus 17 (range 7-84),  $P=0.751$ ) were not statistically different between the semiprone and prone group (Table 3).

**Table 2.** Surgical results

	Before Matching					After Matching				
	Semiprone (n=82)		Prone (n=39)		<i>p</i> value	Semiprone (n=39)		Prone (n=39)		<i>p</i> value
Blood loss (ML)	320	(0-1460)	300	100-680)		388	(197 - 547)		(100-6780)	
								300		
Length of operation (min)	417	(318-547)	235	(147-336)	<0.001	368	(50-1460)		(147 - 336)	<0.001
								225		
Total lymph node yield	18	(5-80)	13	(3-33)	0.001	16	(6-80)	13	(3 -33)	0.019*
R0 resection	77	94%	36	92%	0.685	36	92%	34	92%	0.946
Conversion (total)	7	9%	4	10%	0.896	2	5%	4	10%	0.395
Conversion (thoracic phase)	5	6%	1	3%	0.403	2	5%	1	3%	0.556

**Legend.** Data are expressed as N (%) or median (range). \**P*= 0.128 after exclusion of paratracheally resected lymph nodes.

**Table 3.** Postoperative outcomes

	Before Matching					After Matching				
	Semiprone (n=82)		Prone (n=39)		<i>p</i> value	Semiprone (n=39)		Prone (n=39)		<i>p</i> value
	N		N			N		N		
In-hospital mortality	5	6%	2	5%	0.831	1	3%	2	5%	0.556
Pneumonia	30	37%	14	36%	0.941	19	49%	14	36%	0.252
Pulmonary embolism	2	2%	0	0%	0.325	1	3%	0	0%	0.314
Anastomatic leakage	18	22%	14	36%	0.104	10	26%	14	36%	0.326
Mediastinitis	9	11%	6	15%	0.492	5	13%	6	15%	0.745
Chylothorax	30	37%	11	28%	0.363	15	38%	11	28%	0.337
Laryngeal nerve palsy/injury	6	7%	3	8%	0.941	4	10%	3	8%	0.692
Wound infection	3	4%	3	8%	0.339	2	5%	3	8%	0.644
Arrhythmia	14	17%	10	26%	0.269	6	15%	10	26%	0.262
Myocardial infarction	0	0%	0	0%	-	0	0%	0	0%	-
ICU stay	1	(1-35)	1	(1-30)	0.731	1	(1-16)	1	(1-30)	0.732
Hospital stay	16	(8-87)	17	(7-84)	0.879	18	(8-87)	17	(7-84)	0.751

**Legend.** Data are expressed as N (%) or median (range)



## Discussion

This study represents the first comparison between the semiprone and prone position for thoroscopic mobilization of the esophagus. This study shows that the semiprone position is comparable to a prone position in terms of average estimated blood loss and postoperative complications such as pneumonia. Furthermore, the semiprone position is associated with an at least comparable lymph node yield and a similar percentage of radical resections. This illustrates that the semiprone position is safe and feasible in terms of postoperative complications and radical resections.

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To date, few studies on positioning patients in semiprone position during MIE have been conducted, and most of them are small and descriptive of nature.<sup>13-15</sup> Studies comparing LLD with prone positioning are more common in literature. Recently, an extensive systematic review and pooled analysis on this subject found that prone positioning reduces pulmonary complications, blood loss and increases mediastinal lymph node yield compared to the LLD position.<sup>12</sup> However, this comprehensive review also concluded that further studies are needed to explain performance-shaping factors and their influence on oncological clearance and short-term outcomes. Placing the patient in a semiprone position, hereby combining the benefits of the LLD and prone position, may be one of these performance-shaping factors.

This hypothesis is supported by the first and only comparative study on the feasibility and safety of placing the patient in semiprone position published to date.<sup>16</sup> This study, in which a comparison between the semiprone and LLD position was made, found no statistically significant differences in intra- and postoperative complications. Moreover, the semiprone position was associated with superior surgical ergonomics and better exposure of the posterior mediastinum. These findings, combined with the results of the current study suggest that the profile of postoperative complications following MIE in the semiprone position is comparable to MIE in prone and LLD positioning.

No differences in conversion rates between groups were observed. Although it is a rare event, it has been suggested that if conversion to an open procedure is needed, a thoracotomy is most easily performed when the patient is already in left lateral decubitus position. However, in the current study no severe difficulties were encountered during conversion to thoracoto-

my in either of the approaches. All conversion were performed due to reduced accessibility of the thorax because of adhesions and no emergency conversion was needed. During MIE in semiprone position one can easily tilt the table to mimic the normal position to perform an open thoracotomy.

When conversion to thoracotomy is needed during MIE in prone position the patient needs to be repositioned and draped. However, since no emergency conversion was necessary in our series we did not experience practical problems.

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In the present study, MIE in the semiprone position required more trocar sites (5) than MIE in prone position (4), possibly leading to more surgical trauma for the patient. The semiprone position was associated with an increase in lymph node yield. However, since there is no statistically significant differences in lymph node yield between groups when all paratracheally harvested lymph nodes are excluded from analysis, this finding may rather be attributed to the decision of a more extensive paratracheal lymph node dissection in the semiprone position than to the position itself, possibly at the cost of a somewhat longer operative time. Nevertheless, the current study does show that the semiprone position, unlike the LLD position, does not have to come at the expense of the number of resected lymph nodes. This suggests that the effects of gravity in the prone position do not cease to exist after placing the patient in semiprone position, which reduces the need for lung retractions and gives better exposure of the posterior mediastinum, subcarinal and paratracheal spaces, facilitating not only an extensive lymph node dissection but also the procedure as a whole.[9] Also the absence of deterioration of visibility due to the vertebral column in the semiprone position may further improve lymph node dissection.

There are several limitations to this study. First, all patients in the semiprone position were intubated with a left-side double-lumen tube, while patients in the prone position were ventilated through a single-lumen endotracheal tube. In both the prone and semiprone position both the single-lumen and double-lumen can be used.<sup>17,18</sup> The use of a double-lumen tube allows more controlled emptying of the lung on the operative side, prohibiting the lung to interfere with the operative field while the application of CPAP improves gas exchange, alveolar recruitment, and lung capacity.<sup>19</sup>

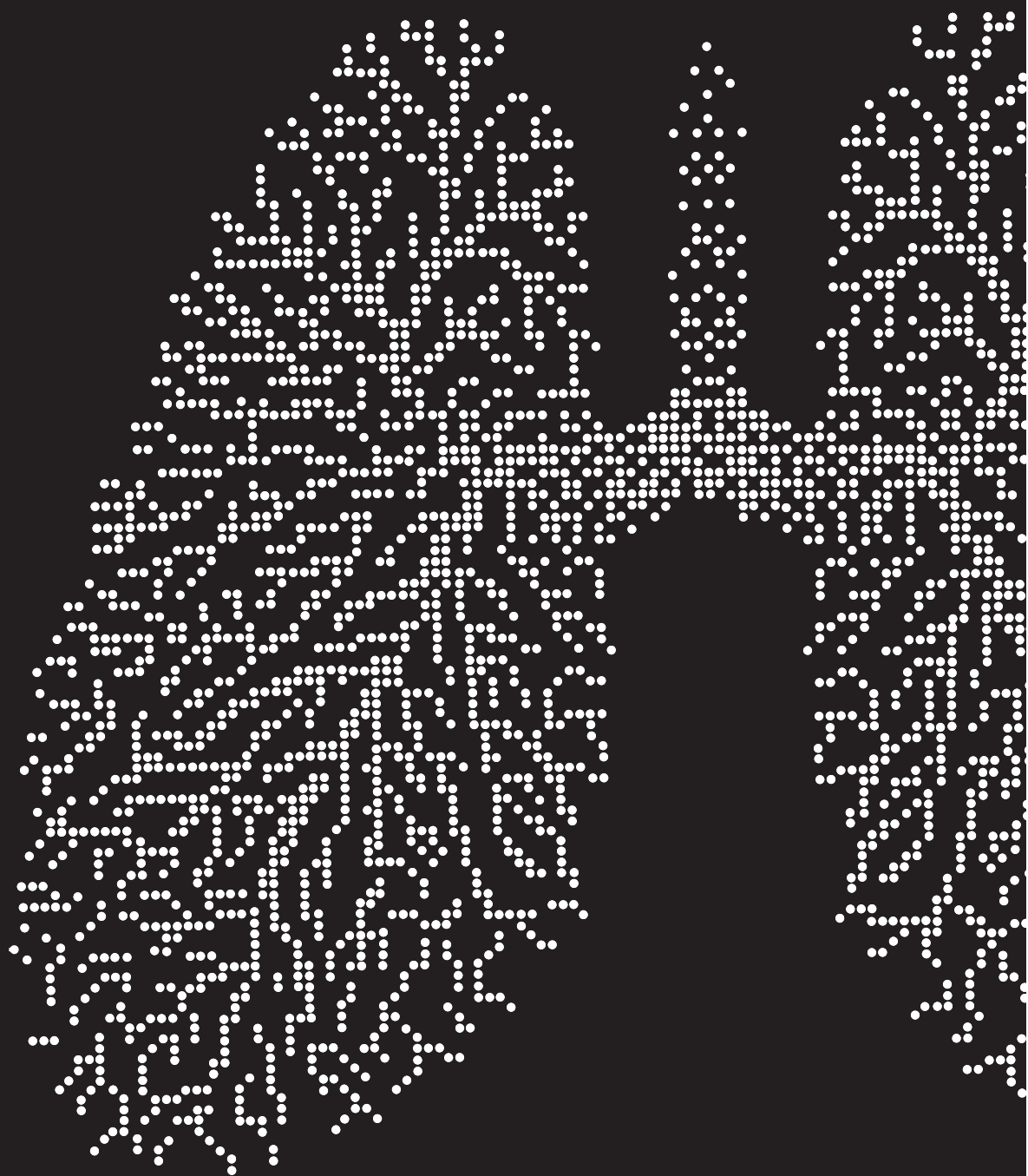
On the other hand, ventilation through a single-lumen endotracheal tube has a distinct benefit in patients requiring prolonged ventilation post-operatively. This method does not require tube change at the conclusion of the procedure, preventing manipulation of the airway and therewith reduces the risk of airway loss and aspiration.<sup>20</sup> However, in the current era of enhanced recovery after surgery programs, most patients are extubated on the day of surgery and only few patients need prolonged ventilation after MIE, therefore this benefit of single lumen tube ventilation is minor. The only studies published to date in which the use of a single-lumen tube is compared with the use of a double lumen in transthoracic MIE report no significant differences in postoperative (pulmonary) complications.<sup>21, 22</sup> Second, despite correction for baseline characteristics through propensity score matching, the inability of propensity score matching to adjust for unknown confounders that could explain some of our findings remains a limitation. Finally, all MIE in semiprone position or prone position were performed in either the University Medical Center Utrecht or the Catharina Hospital Eindhoven, respectively. Although both hospitals provided similar postoperative care, this might have introduced some bias. Nevertheless, inclusion of patients whom are placed in either one of the positions in the same hospital would be very challenging, as in very few hospitals MIE is performed in both positions.

In conclusion, our findings suggest that the semiprone position during MIE is safe, feasible and comparable to MIE in prone position in term of radicality and postoperative complications. Therefore, we would recommend to position the patient according to the surgeons preference.

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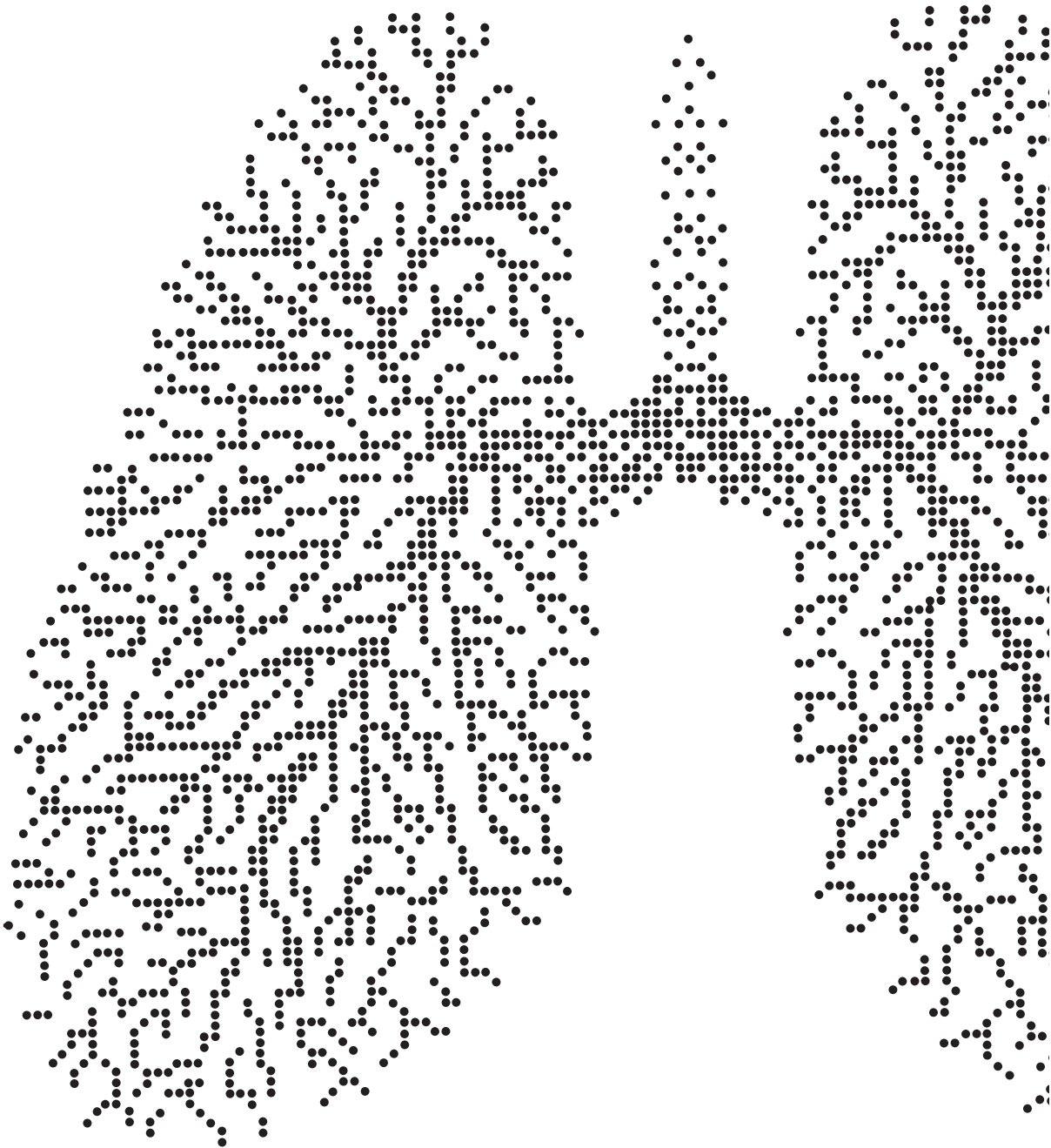
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# **PART II**

## PERIOPERATIVE CARE







# Chapter 6

## Role of selective jejunostomy placement before neoadjuvant chemoradiotherapy in nutritionally ‘at risk’ esophageal cancer patients

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## Abstract

**Background:** The aim of this study was to assess the safety and impact of selective placement of jejunostomy feeding tube (JFT) before neoadjuvant chemoradiotherapy (nCRT).

**Materials & Methods:** Consecutive patients who underwent esophagectomy for cancer following nCRT were included. Patients who received a JFT either before nCRT (early-JFT) or during esophagectomy (delayed-JFT) were compared. Primary endpoints were JFT-related complications and completion of nCRT. Secondary endpoints included nutritional status, postoperative morbidity and 5-year survival.

**Results:** One hundred and thirty three patients were eligible for inclusion in this study: 53 (39.8%) early-JFT and 80 60.2% delayed-JFT. Twenty-five (18.8%) patients had a JFT-related complications. Fifty two (98%) patients in the early-JFT group and 79 (99%) patients in the delayed-JFT group completed all planned cycles of nCRT ( $P=1.000$ ). In the early-JFT group a significantly higher percentage patients were malnourished at diagnosis (greater weight loss  $p<0.001$ , lower body mass index  $P=0.002$ , lower albumin  $P=0.023$ ). Postoperative complications, defined as the occurrence of any complication, did not differ between early- (52%) and delayed-JFT (54%) groups ( $P=0.596$ ). Five-year survival was 35% and 57% in the early- and delayed-JFT groups respectively ( $P=0.033$ ), although patients in the early-JFT group had more advanced disease stage ( $P=0.036$ ). A comparison of stage-matched groups however revealed no statistical difference in survival in patient who recieved with early- or delayed-JFT placement ( $P>0.05$ ).

**Conclusion:** In esophageal cancer patients considered to be at high nutritional risk, JFT placement prior to nCRT for the purpose of supplementary feeding results in equivalent early and late outcomes. In selected patients, early jejunal feeding may therefore help to prevent additional adverse outcomes that are commonly linked to malnutrition in esophageal cancer patients.

## Background

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide, responsible for 439,000 deaths in 2015.<sup>1</sup> Whilst esophagectomy in combination with chemo- and/or radiotherapy remains the mainstay of treatment for patients with localized esophageal cancer, 5-year survival rates in this group seldom exceed 50%.<sup>2</sup>

Poor survival rates that are associated with esophageal cancer are frequently ascribed to the late stage at which patients typically present as well as a preponderance to early lymphovascular invasion. There is now however growing appreciation that patients nutritional status may also play a significant role in influencing outcomes of esophageal cancer.<sup>3-7</sup> Weight loss is ubiquitous in patients treated for esophageal cancer and is associated with multiple factors pertaining to elevated energy expenditure and anorexia that are related to the tumour itself, the effects of multimodal therapy as well as direct obstruction of the upper gastrointestinal tract.<sup>3,4</sup> Anorexia and the ability to maintain adequate nutritional intake is an important prognostic factor and is present in approximately 30% of esophageal cancer patients at diagnosis, moreover further 30% of patients develop anorexia during neoadjuvant chemoradiotherapy (nCRT).<sup>3,4,8,</sup>

Supplementary enteral feeding is often initiated during nCRT to increase caloric intake, however for those reasons given above, patients frequently struggle to meet their nutritional requirements via an oral route alone. Whilst nasogastric and nasojejunal feeding tubes offer an alternative mode for feeding, poor patient acceptance and frequent displacement, limit their widespread usage.<sup>9</sup> Placement of percutaneous jejunal feeding tubes (JFT), although routine practice in some centers at the time of tumor resection is seldom considered as an early intervention to prevent worsening malnutrition during neoadjuvant therapy. Concern regarding high rates of morbidity that have been associated with JFT in some series has served as a major factor limiting their wider use in this patient population.

It is hypothesized that initiation of nutritional support by JFT prior to nCRT is a safe alternative to existing methods of nutritional supplementation that will prevent additional weight loss and improve both adherence to nCRT and postoperative outcomes. The aim of this study was therefore to assess the safety and impact of selective placement of JFT before nCRT and

to compare outcomes to patients who had delayed-JFT placement at the time of esophageal resection.

## Materials & Methods

Prior ethical approval was granted for the current study, with the medical ethic committee waiving the requirement for informed consent to be obtained for use of anonymized patient data.

### Patients and data

Patients were identified from an institutionally approved prospective database of consecutive patients undergoing esophagectomy at Virginia Mason Medical Center between January 2009 and January 2016. Inclusion criteria were, patients with biopsy proven esophageal cancer who received nCRT and JFT placement either before nCRT (early-JFT) or at the time of esophagectomy (delayed-JFT). Standard nCRT regimens consisted of five cycles of either Carboplatin and Taxol or Cisplatin and Fluorouracil with concurrent radiation therapy given, typically at a dose of 50.4 Gy over 28 fractions. Timing of JFT placement was determined in accordance with the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines.<sup>10</sup> Patients who presented with  $\geq 2$  of the following features: weight loss  $>10\%$  in the past 3 months; body mass index (BMI)  $<18.5 \text{ Kg/m}^2$ ; dysphagia to all solids; Eastern Cooperative Oncology Group (ECOG) scale of performance status of  $\geq 2$ , or; Albumin level  $<3.25\text{g/dl}$ , were considered for JFT placement before nCRT. In all patients who did not meet these criteria, JFT placement was delayed until the time of definitive surgery. All patients were discussed within an institutional multidisciplinary tumor board, which was responsible for making the final recommendation as to the timing of JFT placement. The JFT typically remained in-situ for three months after esophagectomy. During the period in which the JFT was in place the patient would follow the dietary plan according to our institutional standardized clinical pathway for esophagectomy that are based on ASPEN guidelines.<sup>10,11</sup> Patients who received delayed JFT placement, during their nCRT they received individualized dietary monitoring and oral nutritional supplementation when clinically indicated.

For patient meeting the inclusion criteria for the current study additional data relating to nutritional status were retrospectively collected from computerized medical records.

### Surgical technique for JFT placement

JFT placement prior to nCRT was performed via a small supraumbilical incision (2-3cm). A

loop of jejunum approximately 40-80cm distal to the ligament of Treitz was identified and exteriorized. A 14 Fr feeding tube (Jejunal Feeding “MIC” tube, Halyard Health, Alpharetta, GA, USA) cut to approximately 30-40cm length was introduced in to the jejunal lumen through the antimesenteric border of the bowel. After inflating the JFT balloon with 2ml saline it was secured with a pursestring suture and 2cm Witzel tunnel. The JFT was then brought out through the abdominal wall lateral to the incision and the jejunum was fixed to the parietal peritoneum by 4 sutures placed circumferentially around the point of insertion. Three point fixation between the jejunum and peritoneum was achieved by placing additional sutures 4cm proximal and distal to the site of jejunostomy with the intention to reduce the risk intestinal volvulus. External fixation of the JFT was achieved by suturing to the skin. With the exception of surgical access this procedure was the same for delayed JFT placed at the time of definitive surgery.

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### Outcomes

The primary outcomes of the current study were jejunostomy related complications as well as completion of nCRT.<sup>12,13</sup> Secondary outcomes included post-operative complications, nutritional status at follow up, histological response to neoadjuvant therapy and overall survival.<sup>14,15</sup>

### Statistical analyses

Data were analyzed using R 3.1.2 open-source software (<http://www.R-project.org>) and SPSS for windows, version 22.0 (IBM corp., Armonk, New York) Patient and treatment-related characteristics and outcomes were compared between to the early-JFT and delayed-JFT group. Categorical data were compared using the chi-square test or Fisher’s exact test in case of small cell counts. Continuous data were compared using the Mann-Whitney-U test (non-parametric variables) or Student’s T-test (parametric variables). Kaplan-Meier curves were used to assess overall survival, and differences between the groups were evaluated using the log-rank test.

## Results

### Baseline and treatment characteristics

In total 133 patients met the inclusion criteria for the current study. Fifty-three (39.8%) patients underwent early-JFT placement prior to starting nCRT and 80 (60.2%) underwent JFT placement during esophagectomy (Table 1). In keeping with criteria for placement of JFT prior to nCRT patients who received this intervention had significantly higher incidence of dysphagia ( $P<0.001$ ), greater mean weight loss ( $P<0.001$ ), lower BMI ( $P=0.002$ ) and lower albumin level ( $P=0.023$ ) at diagnosis compared to patient who underwent delayed-JFT placement (Table 1). Patients in the early-JFT group also tender to have a higher ECOG performance status and more advanced disease ( $P<0.05$ ).

**Table 1.** Patient characteristics

	Total (n=133)	Early JTF (n=53)	Delayed JTF (n=80 )	<i>P value</i>
<b>Gender</b>				
Female	28 (21.1)	13 (24.5)	15 (18.8)	0.424
Male	105 (68.9)	40 (75.5)	65 (81.2)	
<b>Age (year)</b>	65.5±9.6	66.0 ±9.7	65.2 (9.6)	0.629
<b>BMI at diagnosis</b>	27.0±4.5	26.0 ±4.1	27.5±4.5	0.002
<b>History of weight loss</b>	75 (56.4)	44(83.0)	31 (38.8)	<0.001
<b>Weight loss at diagnosis</b>	4.9±6.2	7.9±6.5	3.1±5.3	<0.001
<b>BMI at diagnosis</b>	27.0±4.5	26.0 ±4.1	27.5±4.5	0.002
<b>ECOG</b>				
O	70 (52.6)	22 (41.5)	48 (60.0)	0.039
I	49 (44.4)	29 (54.7)	30 (37.5)	
II	4 (3.0)	2 (3.8)	2 (2.5)	
<b>ASA score</b>				
II	55 (41.4)	18 (34.0)	37 (46.3)	0.159
III	78 (58.6)	35 (66.0)	43 (53.7)	
<b>History of smoking</b>	110 (82.7)	44 (83.0)	66 (82.5)	0.938
<b>Comorbidity</b>				
Cardiac	28 (21.1)	12 (22.6)	16 (20.0)	0.714
Vascular	66 (49.6)	26 (49.1)	40 (50.0)	0.915
Diabetes	25 (18.8)	7 (13.2)	18 (22.5)	0.179
Asthma	11 (8.3)	4 (7.5)	7 (8.8)	0.805
COPD	12 (9.0)	4 (7.5)	8 (10.0)	0.629

**Table 1 continued.** Patient characteristics

	Total (n=133)	Early JTF (n=53)	Delayed JTF (n=80)	P value
<b>Clinical stage</b>				
IA	1 (0.8)	0 (0.0)	1 (1.3)	0.001
IB	0 (0.0)	0 (0.0)	0 (0.0)	
IIA	3 (2.3)	2 (3.8)	1 (1.3)	
IIB	42 (31.6)	8 (15.1)	34 (42.5)	
IIIA	75 (56.4)	33 (62.3)	42 (52.5)	
<b>Clinical stage</b>				
IIIB	10 (7.5)	9 (17.0)	1 (1.3)	0.461
IIIC	2 (1.5)	1 (1.9)	1 (1.3)	
<b>Histology</b>				
Adenocarcinoma	115 (86.5)	45 (84.9)	70 (87.5)	
SCC	17 (12.8)	7 (13.2)	17 (21.3)	
Other	1 (0.8)	1 (1.9)	0 (0.0)	
<b>Surgical approach</b>				
2 / 3* Stage	62 (46.7)	22 (41.5)	40 (50.0)	0.337
Left-TA	71 (53.3)	31 (58.5)	40 (50.0)	
<b>Gastric conduit</b>	132 (99.2)	52 (98.1)	80 (100.0)	0.217
<b>Operative time (min)</b>	401±40	384±39	412±59	0.007

Values in parentheses are percentages. For continuous variables data shown represent median (interquartile range).

**Abbreviations:** JFT, percutaneous jejunal feeding tube. BMI, body mass index. ECOG, Eastern Cooperative Oncology Group. ASA, American Society of Anaesthesiologist. COPD, chronic obstructive pulmonary disease. SCC, squamous cell carcinoma. TA, thoracoabdominal. 2 / 3-stage, two or three stage esophagectomy. \*5 patients underwent three-stage esophagectomy (early-JFT n=3; delayed-JFT, n=2)

### Jejunostomy-related outcomes

Median hospital stay after early-JFT placement was 1 (range, 1-4) day. Two (3.8%) out of 53 patients in the early-JFT group had postoperative ileus after tube placement. There were no further intra- or immediate post-operative complications following early-JFT placement. The duration of esophageal resection was significantly longer in the delayed-JFT group when compared to the early-JFT group (Table 1,  $P=0.007$ ). In both groups all patients utilized the JFT at the time of discharge following esophagectomy.

A total of 25 (18.8%) jejunostomy related complications were observed across the entire study cohort (Table 2). The percentage of JFT related complications were not significantly different between patients who received either early- (n=9, 17%) or delayed-JFT (n=16,



20%) placement ( $P=0.821$ ). No complications associated with JFT led to either Intensive Care Unit (ICU) admission or mortality. In 3 (2%) patients the JFT was not replaced after dislodgement as they were deemed to be consuming an adequate oral diet at that time.

Patients in the early-JFT group gained an average of  $0.1\pm 9.3\%$  of their weight at diagnosis during neoadjuvant therapy, while patients in the delayed-JFT group lost on average  $3.1\pm 23.8\%$  of their weight at diagnosis ( $P=0.101$ ). At three months following esophagectomy patients in the early-JFT group had lost on average  $7.5\pm 23.8\%$  of their body weight at surgery compared to  $6.1\pm 9.1\%$  who underwent delayed-JFT placement ( $P=0.408$ ).

**Table 2.** Jejunostomy related complications

	(n=133)
<b>Total number of complications</b>	25 (18.8)
<b>Patient-related complications</b>	
Bloating	3 (2.3)
Pain	1 (0.8)
Site-infection	2 (1.5)
<b>Tube-related complications</b>	
Blockage	2 (1.5)
Dislodgement	17 (12.7)
<b>Clavien Dindo grade</b>	
grade 1	10 (7.5)
grade 2	2 (1.5)
grade 3a	13 (7.5)
grade 3b	3 (2.3)
<b>Required interventions</b>	
No intervention	4 (3.0)
Replacement	12 (9.0)
Removal	4 (3.0)
Topical medicine or antibiotic	2 (1.5)
Analgesia	1 (0.8)
Irrigation	1 (0.8)
Drainage	1 (0.8)

*Values in parentheses are percentages.*

### Completion of nCRT

One hundred and thirty-one (98.5%) patients completed neoadjuvant chemoradiotherapy as prescribed, with a single patient in each group failing to complete the intended therapy ( $P=1.000$ ).

### Postoperative and histopathological outcomes

There was no significant difference in the percentage of patients who developed a non JFT-related complication after esophagectomy (Table 3). The total number of patients who developed at least 1 complication was 26 (49.1%) in early-JFT group vs. 43 (53.8%) in the delayed-JFT group ( $P=0.596$ ). There were no in-hospital deaths or deaths within 90-days of surgery. There was no significant difference in either the length of ICU ( $P=0.519$ ) or hospital ( $P=0.225$ ) stay in both groups.

**Table 3.** Clinical outcomes

	Total (n=133)	Early JTF (n=53)	Delayed JTF (n=80 )	P
<b>Completion of nCRT</b>	131 (98.5)	52 (98.1)	79 (98.8)	1.000
<b>Postoperative complication</b>	69 (51.9)	26 (49.1)	43 (53.8)	0.596
Pneumonia	11 (8.3)	4 (7.5)	7 (8.5)	0.805
Pneumothorax	18 (13.5)	7 (13.2)	11 (13.8)	0.929
Pleural effusion	16 (12.0)	7 (13.2)	9 (11.3)	0.734
Reintubation	5 (3.8)	4 (7.5)	1 (1.3)	0.062
Anastomotic leakage	9 (6.8)	2 (3.8)	7 (8.8)	0.263
Chyle leakage	7 (5.3)	2 (3.8)	5 (6.3)	0.531
RLN injury	0 (0.0)	0 (0.0)	0 (0.0)	-
Atrial fibrillation	28 (21.1)	10 (18.9)	18 (22.5)	0.615
<b>Length of ICU admission</b>	1 (0-30)	1 (1-3)	1 (0-30)	0.519
<b>Length of hospital admission</b>	7 (5-115)	7 (5-115)	7 (5-45)	0.225
<b>Readmission (90-day)</b>	25 (18.8)	10 (18.9)	15 (18.8)	0.986
<b>Mortality (30-day)</b>	0 (0.0)	0 (0.0)	0 (0.0)	-

*Values in parentheses are percentages or range. Abbreviations JFT, percutaneous jejunal feeding tube. nCRT, neoadjuvant chemoradiotherapy. RLN, recurrent laryngeal nerve. ICU, intensive care unit*

The 90-day readmission rate after esophagectomy was similar between patients who had undergone either early (n=10, 18.9%) or delayed (n=15, 18.8%) JFT placement ( $P=0.986$ ). In each group two patients were readmitted as a consequence of a dislodged JFT whilst one

further patient from both the early- and delayed-JFT groups were readmitted with bloating and a jejunostomy site infection respectively.

Histopathological outcomes are shown in Table 4. Patient who underwent early-JFT placement tended to have more advanced pathological tumor (T) stage and overall cancer stage compared to patients in the delayed-JFT group ( $P<0.05$ ). Nodal and tumor metastasis status, lymph node harvest and R0 resection rate were not however significantly different between groups.

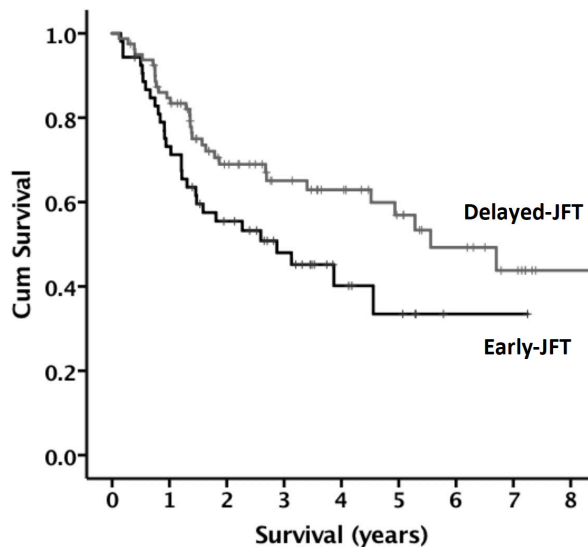
**Table 4.** Histopathological characteristics

	Total (n=133)	Early JTF (n=53)	Delayed JTF (n=80 )	P
<b>Lymph node yield</b>	20 (5-45)	20 (10-35)	20 (5-45)	0.721
<b>Pathological T-status</b>				
pCR	33 (24.8)	10 (18.9)	23 (28.7)	0.044
T1	18 (13.5)	4 (7.5)	14 (17.5)	
T2	24 (18.0)	11 (20.8)	13 (16.3)	
T3	58 (43.6)	28 (52.8)	30 (37.5)	
T4	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Pathological N-status</b>				0.087
N0	70 (52.6)	25 (47.2)	45 (56.3)	
N1	31 (23.3)	10 (18.9)	21 (26.3)	
N2	21 (15.8)	10 (18.9)	11 (13.8)	
N3	11 (8.3)	8 (15.1)	3 (3.8)	
<b>Pathological M-status</b>				
M0	132 (99.2)	52 (98.1)	80 (100)	0.217
M1	1 (0.8)	1 (1.9)	0 (0.0)	
<b>R1</b>	4 (3.0)	2 (3.8)	2 (2.5)	
<b>Pathological stage</b>				
0*	25 (18.8)	7 (13.2)	18 (22.5)	0.037
IA	8 (6.0)	2 (3.8)	6 (7.5)	
IB	10 (7.5)	4 (7.5)	6 (7.5)	
IIA	12 (9.0)	9 (17.0)	3 (3.8)	
IIB	30 (22.6)	8 (15.1)	22 (27.5)	
IIIA	16 (12.0)	5 (9.4)	11 (13.8)	
IIIB	19 (14.3)	10 (18.9)	9 (11.3)	
IIIC	13 (9.8)	8 (15.1)	5 (6.3)	

Values in parentheses are percentages. \*Signifies complete pathological response to neoadjuvant chemoradiotherapy therapy.

### Survival Outcomes

Median follow-up after esophagectomy was 25 (range, 1-93) months. Five-year survival was significantly lower in patients who underwent early JFT placement group when compared to patients the JFT placement at the time of esophagectomy (34% vs. 57%;  $P=0.036$ )(Figure 1). After matching for pathological stage (0/I/II/III) survival differences were no longer significant ( $p>0.05$ )



**Figure 1.** Kaplan-Meier analysis of overall survival for patients who underwent either early- or delayed- jejunal feeding tube (JFT) placement ( $P=0.036$ )

## Discussion

Esophageal cancer is frequently associated with increased energy metabolism and dysphagia, increasing the risk of malnutrition. Several studies have shown that a poor nutritional status at diagnosis is associated with an increase in postoperative complications and reduced survival<sup>3-7</sup>, highlighting the need for adequate early evaluation and management of malnutrition in patients with esophageal cancer. The interval between diagnosis and definitive surgery, which is often prolonged by the provision of nCRT, must be recognized as the opportune moment to correct nutritional deficiency.<sup>16</sup>

The principal findings of the current study were that early-JFT placement was associated with acceptable morbidity and high rates of completion of nCRT in patients who were considered to be physiologically and nutritionally at 'high-risk'. It is specifically noted that the increased duration of feeding tube placement in those patient's receiving this intervention prior to nCRT was not associated with a greater number of complications suggesting that morbidity is unrelated to the length of use, but rather to technical factors relating to formation and safe management. In contrast to previous reports and despite differences in nutritional status at diagnosis, no significant differences in morbidity and length of hospital stay after esophagectomy were observed between the early and delayed JFT groups in the current study.

There currently exists limited data relating to the percentage of patients who fail to proceed to surgery following nCRT. The only study providing specific data on this issue is the CROSS trial, in which 3/171 (1.8%) did not undergo surgery after nCRT.<sup>16</sup> However, this may be an underestimation of the true percentage, since patients included in randomized control trials typically have a better performance status when compared to an unselected population.<sup>17</sup> In the current study, despite evidence of malnutrition at the time of diagnosis, only a single patient who received early jejunal feeding was unable to complete all planned cycles of nCRT. This is in contrast to the results of previous studies in which patients, who did not receive a JFT prior to nCRT, were reported to have completion rates of 78-91% for all cycles of chemotherapy and 91-99% for all cycles of radiotherapy.<sup>8,18</sup> Moreover, these patients received a dose of 41.4 Gy, whilst in the current study patients typically received a dose of 50.4 Gy. In one study that reported outcomes after definitive chemoradiotherapy, in selective patients completion rates were <40%.<sup>19</sup>

In contrast to previous reports, and despite the difference in nutritional status at diagnosis, no significant differences in morbidity and length of hospital stay after esophagectomy were observed between the early- and delayed-JFT groups in the current study. This strongly supports that the poor nutritional status at diagnosis was appropriately addressed by JFT feeding, as reflected by the prevention of further weight during nCRT even in an 'at risk' population. These findings, in combination with the observation that JFT-related complications did not increase over time, supports the premise that a JFT should be considered in esophageal cancer patients who are nutritionally 'at risk' prior to nCRT. Whilst overall 5-year survival rate was significantly lower in patients who underwent early-JFT placement, a greater proportion of this group had more advanced disease by both clinical and pathological staging. Survival difference was however no longer significant after matching patients by pathological stage. Equivalent survival between stage-matched groups could suggest that

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The incidence of JFT-related complications varies widely in the current literature and has been reported to occur in up to 39% of patients.<sup>9</sup> The severity of the complications is variable and most often involves dislodgement, surgical site infection, and intraperitoneal leak.<sup>4,20-25</sup> Mortality rates up to 9.6% have been reported, although generally in older studies.<sup>26-28</sup> Due to the variability in reported outcomes, controversy remains regarding the role of JFT placement in both at the time of diagnosis and definitive surgery. In one study, of 143 patients who had a JFT placed at the time of esophagectomy, only 33 (23.1%) were utilizing it for additional nutritional support at the time of hospital discharge whilst 26 patients (18.2%) had a JFT-related complication.<sup>21</sup> The only predictor for JFT utilization identified by the authors was a BMI <18.5. If nothing else this study highlights the importance of clear guidelines for the insertion and use of JFT's in the context of esophageal cancer. Such guidelines must recognize the importance of judicious patient selection and the timing of intervention. Furthermore, appropriate consideration should be given to technical aspects of JFT that may potentially reduce complication. Utilization of a medial entry site for the JFT and fixing the bowel in at least three locations have been suggested to reduce the incidence of intestinal volvulus.<sup>20</sup> Small tube sizes may also reduce rates of bowel obstruction.<sup>20</sup> A tube size of 14 Fr was used in the current study, which is believed to decrease the incidence of tube-related complications, including blockage. Furthermore the

balloon was never inflated with more than 2ml of saline.

This study suffers from some important limitations. Only patients who were nutritionally ‘at risk’ received a JFT before nCRT whilst patients in the delayed-JFT group received individual dietary monitoring and support as required. Data utilized in the current study were also derived from a surgical database, meaning that no information regarding patients who started nCRT but did not proceed to surgery were available introducing a further potential source of selection bias. Accordingly, the results of the current study may be an overestimation of the beneficial effect of JFT placement before nCRT. Finally, measures of nutrition including weight, BMI and Albumin that are used in this and many other studies are generally considered insufficient to provide accurate assessment of this outcome. An alternative method of assessing nutrition that has recently shown promise is the use CT for the measurement of body composition (skeletal muscle and adipose tissue).<sup>29</sup> Future studies may there wish to consider the adoption of such technique to support more accurate nutritional assessment.

JFT supports nutrition during trimodality therapy for esophageal cancer and JFT-related complications are typically minor. Postoperative outcomes of patients who were malnourished at diagnosis and received a JFT before nCRT were equivalent to the postoperative outcomes in non-malnourished patients including long-term survival.

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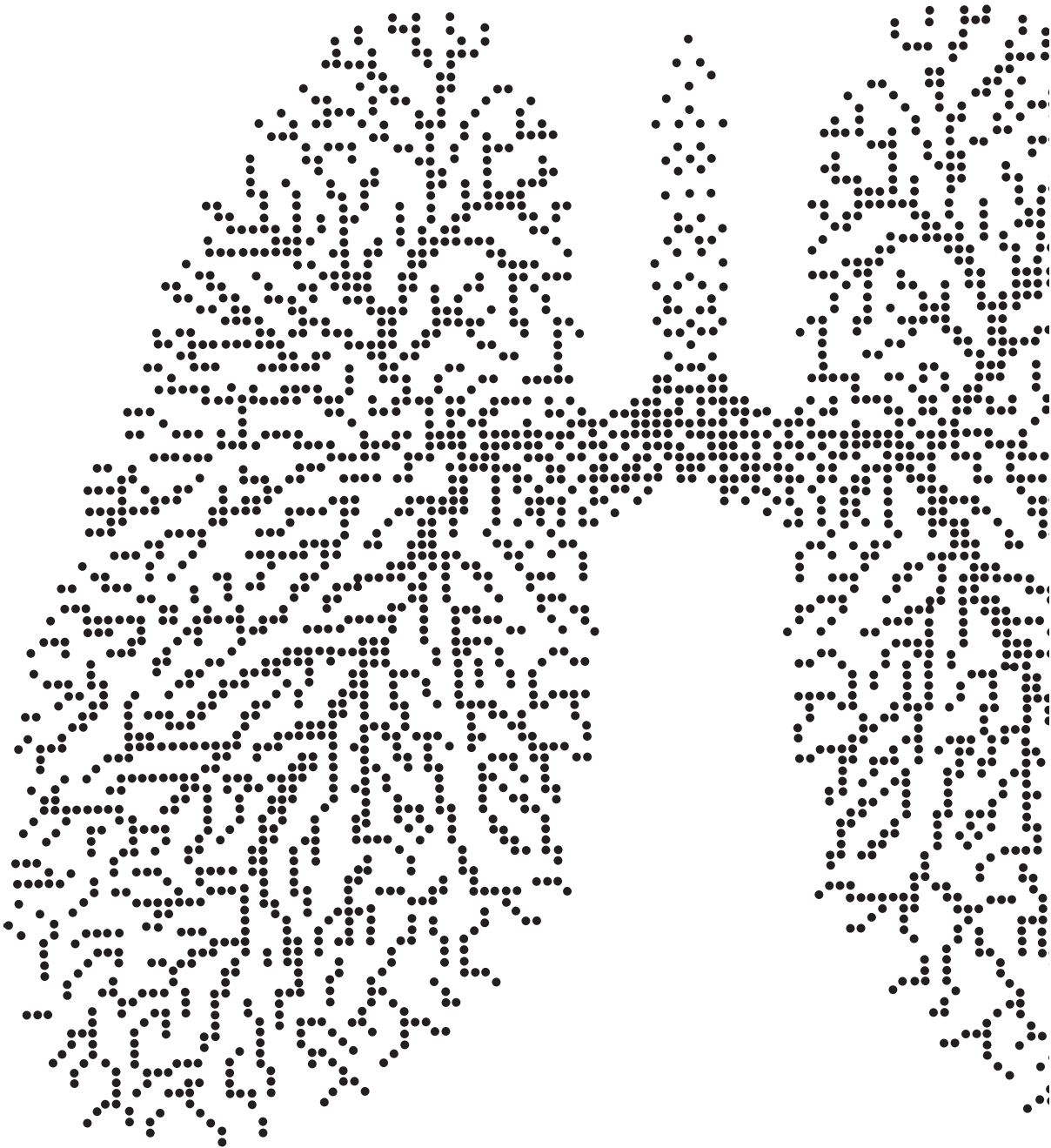
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# Chapter 7

## Recurrent laryngeal nerve injury after esophagectomy for esophageal cancer: Incidence, management, and impact on short- and long-term outcomes

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## Abstract

**Background:** Recurrent laryngeal nerve injury caused by esophagectomy may lead to post-operative morbidity, however data on long-term recovery are scarce. The aim of this study was to evaluate the consequences of recurrent laryngeal nerve palsy (RLNP) in terms of pulmonary morbidity and long-term functional recovery.

**Materials & Methods:** Patients who underwent a 3-stage transthoracic (McKeown) or a transhiatal esophagectomy for esophageal carcinoma in the University Medical Center Utrecht between January 2004 and March 2016 were included from a prospective database. Multivariable analyses were conducted to assess the association between RLNP and pulmonary complications and hospital stay. Data regarding long-term recovery were summarized using descriptive statistics.

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**Results:** Out of the 451 included patients, 47 (10%) were diagnosed with RLNP. Of the patients with RLNP, 34 (7%) had a unilateral lesion, 8 (2%) had bilateral lesions, and in 5 (1%) the location of the lesion was unknown. The incidence of RLNP was 3/127 (2%) in the transhiatal group, and 44/324 (14%) in the McKeown group. RLNP after McKeown esophagectomy was associated with a higher incidence of pulmonary complications (OR 2.391; 95% CI 1.222-4.679;  $p=0.011$ ), as well as a longer hospital stay (+4 days) ( $p=0.001$ ). Of the RLNP patients with more than 6 months follow up almost half recovered fully (median follow-up of 17.5 months (7-135)). Of the remainder, 6 required a surgical intervention and the others had residual symptoms.

**Conclusions:** RLNP after McKeown esophagectomy is associated with an increased pulmonary complication rate, longer hospital stay, and a moderate long-term recovery. Further studies are necessary that examine technologies which may reduce RLNP incidence and may contribute to the early detection and treatment of RLNP.

## Background

Esophageal cancer is the eighth most common type of cancer worldwide, and its incidence is rising.<sup>1-3</sup> The current standard of care for patients with a resectable locally advanced tumor is neoadjuvant chemo(radio)therapy, followed by surgical resection with a radical lymphadenectomy.<sup>4-6</sup>

During esophagectomy, thermal injury, stretching, compression, or vascular compromise of the recurrent laryngeal nerve (RLN) may cause RLN palsy (RLNP).<sup>7</sup> The incidence of RLNP after esophagectomy varies, ranging from 0% to 59%.<sup>8-18</sup> These disparities have been attributed to variation in extent of lymph node dissection, surgical technique (two- or three stage), the size and T-stage of the primary tumor, and the means of recurrent laryngeal nerve injury diagnosis.<sup>8,19-21</sup>

In addition to being the most important motor nerve of the larynx, the RLN innervates the cricopharyngeal muscle which form the upper esophageal sphincter, hereby playing a central role in swallowing.<sup>22</sup> Patients with RLNP may present with symptoms ranging from hoarseness, dyspnea during speech, aspiration, difficulty with coughing, marked morbidity through pulmonary complications (pneumonia, ARDS, atelectasis), and may even suffocate in case of bilateral damage. Only few retrospective studies have reported on the consequences of RLNP on the short term, particularly the incidence of pulmonary complications.<sup>8-10,19,23,24</sup> Furthermore, information on the long term (i.e. recovery and possible surgical interventions) is lacking. Therefore, the current study aims to evaluate the consequences of RLNP in terms of (pulmonary) morbidity and long-term functional recovery.

## Methods

### Patients

This cohort study used a prospective database of the University Medical Center Utrecht (UMCU) to include patients who underwent a 3-stage transthoracic (McKeown) or transhiatal esophagectomy with a gastric conduit reconstruction for esophageal carcinoma between January 2004 and March 2016. Specific follow-up data regarding RLNP were supplemented from the electronic patient record. This study received ethical approval (Institutional Review Board number 13-061/C) from the Medical Ethics Review Committee of the UMCU, and informed consent was waived.

### Outcomes

Primary outcome was the association of RLNP and postoperative pulmonary complications. To create a homogeneous cohort for analyzing the association between RLNP and postoperative pulmonary complications, only the McKeown esophagectomies were included. RLNP was defined as any kind of damage inflicted during surgery to the left, the right, or both of the recurrent laryngeal nerve(s), resulting in paresis or paralysis. Paresis was defined as a partial interruption of laryngeal innervation, leading to hypomobility of the laryngeal muscles. Paralysis was defined as no motion of the affected muscle(s).<sup>25</sup> Pulmonary complications were defined as clinically proven pneumonia (in accordance with the revised Uniform Pneumonia Score,<sup>26</sup> pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome (ARDS), atelectasis, re-intubation, or the need for a tracheostomy.

Secondary outcomes were otolaryngological consultation for RLNP, clinical presentation of the RLNP (dysphonia and/or aspiration), means of RLNP diagnosis (clinical or laryngoscopic), and RLNP-specific therapy and functional recovery. For functional recovery, only people with a follow-up of at least 6 months at the time of data extraction were included, because RLNP recovery may not have occurred before that time.<sup>27</sup> Complete recovery from RLNP symptoms, possibly with laryngoscopy showing full revival of vocal cord mobility, was seen as full recovery.

Clinical improvement of RLNP symptoms, possibly with laryngoscopy showing some improvement of vocal cord mobility, was seen as partial recovery. No improvement of RLNP



symptoms, possibly with laryngoscopy showing no improvement of vocal cord mobility, was seen as no recovery. Other secondary outcomes included re-intervention, 30-day postoperative or in-hospital mortality, intensive care unit (ICU) and hospital stay in days, readmission within 30 days, non-radical resection, and anastomotic leakage.

### Statistics

All data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM corp., Armonk, New York, USA). All continuous data were presented as median (range) or mean ( $\pm$  standard deviation (SD)) based on their distribution; all categorical data were presented as a number (percentage). Baseline data were analyzed using either chi-square tests (categorical data), Mann-Whitney-U tests, or student's t-test (continuous data). Multivariable logistic and linear analyses were conducted to assess the association between RLNP and pulmonary complications and hospital stay, respectively. All variables with a p-value  $<0.2$  in univariable analysis were entered in the multivariable analyses and a p-value of  $<0.05$  was considered statistically significant.

## Results

### Patients

Between January 2004 and March 2016 324 underwent a 3-stage transthoracic (McKeown) esophagectomy with a two-field lymphadenectomy and 127 patients underwent a transhiatal esophagectomy for esophageal carcinoma (Figure 1). The baseline data showing patient and treatment-related characteristics for the McKeown group is provided in Table 1. The mean (SD) age was 65 ( $\pm 8.53$ ) years, 72% of the patients were male, most (61%) had an ASA II status and 51% were diagnosed with a pT3 tumor. The majority (82%) of patients underwent robot-assisted thoracoscopic minimally invasive surgery (da Vinci Si System, Intuitive Surgical Inc., Sunnyvale, CA, USA), the other 58 (18%) underwent open surgery.

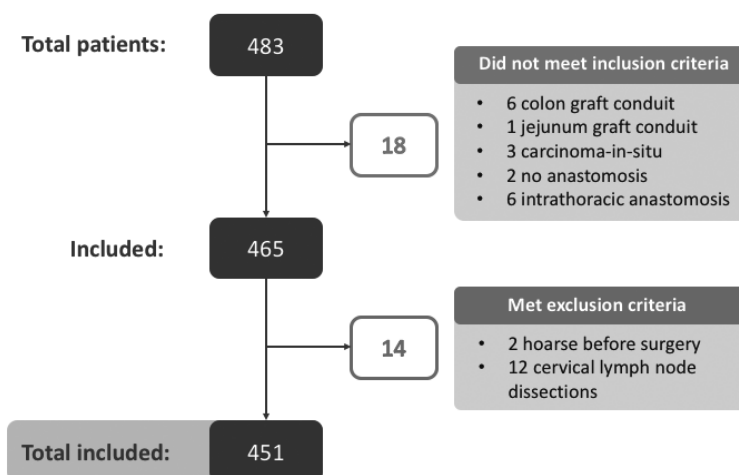
**Table 1.** Patient and treatment-related characteristics

Characteristic		Total (n=324)		RLNP+ (N=44, 13.6%)		RLNP- (N=280, 86.4%)		<i>p</i> value
		n	(%)	n	(%)	n	(%)	
<b>Gender</b>	Female	91	28.1%	13	29.5%	78	27.9%	0.817
	Male	233	71.9%	31	70.5%	202	72.1%	
<b>Age (years)</b>		64.5	$\pm 8.53$	63.5	$\pm 8.93$	65.0	$\pm 8.48$	0.523
<b>BMI (kg/m<sup>2</sup>)</b>		25.0	$\pm 4.42$	25.1	$\pm 3.86$	25.0	$\pm 4.50$	0.864
<b>ASA score</b>	I	83	25.6%	13	29.5%	70	25.0%	0.861
	II	199	61.4%	24	54.5%	175	62.5%	
	III	42	13.0%	7	15.9%	35	12.5%	
<b>Pulmonary comorbidity</b>	No	272	84.0%	37	84.1%	235	83.9%	0.978
	Yes	52	16.0%	7	15.9%	45	16.1%	
<b>Cardiac comorbidity</b>	No	259	79.9%	41	93.2%	218	77.9%	0.018
	Yes	65	20.1%	3	6.8%	62	22.1%	
<b>Vascular comorbidity</b>	No	247	76.2%	38	86.4%	209	74.6%	0.090
	Yes	77	23.8%	6	13.6%	71	25.4%	
<b>Diabetes mellitus</b>	No	284	87.7%	40	90.9%	244	87.1%	0.480
	Yes	40	12.3%	4	9.1%	36	12.9%	
<b>Neoadjuvant treatment</b>	No	95	29.3%	15	34.1%	80	28.6%	0.328
	Chemotherapy	85	26.2%	14	31.8%	71	25.4%	
	Chemoradiotherapy	144	44.4%	15	34.1%	129	46.1%	
<b>Approach</b>	Open	58	17.9%	4	9.1%	54	19.3%	0.101
	Minimally invasive	266	82.1%	40	90.9%	226	80.7%	

**Table 1 continued.** Patient and treatment-related characteristics

Characteristic		Total (n=324)		RLNP + (N=44, 13.6%)		RLNP- (N=280, 86.4%)		
<b>Location of Tumor</b>	proximal	12	3.7%	1	2.3%	11	3.9%	0.709
	middle	53	16.4%	9	20.5%	44	15.7%	
	distal	122	37.8%	14	31.8%	108	38.6%	
	GEJ	137	42.3%	20	45.5%	117	41.8%	
<b>Histology</b>	ADC	227	69.8%	33	75.0%	194	69.3%	0.203
	SCC	95	29.0%	10	22.7%	85	30.4%	
	Other	2	0.6%	1	2.3%	1	0.3%	
<b>pT stage</b>	T0	59	18.2%	4	9.1%	55	19.6%	0.044
	T1	43	13.3%	5	11.4%	38	13.6%	
	T2	45	13.9%	5	11.4%	40	14.3%	
	T3	165	50.9%	28	63.6%	137	48.9%	
	T4	12	3.7%	2	4.5%	10	3.6%	
<b>pN stage</b>	N0	154	47.6%	16	36.4%	137	48.9%	0.233
	N1	85	26.2%	16	36.4%	69	24.6%	
	N2	58	17.9%	7	15.9%	51	18.2%	
	N3	27	8.3%	5	11.4%	23	8.3%	
<b>Lymph node yield*</b>	median, range	22	(6-57)	24,5	(7-57)	22,0	(6-53)	<0.001
<b>Radical resection</b>	Yes	296	91.4%	38	86.4%	258	92.1%	0.205
	No	28	8.6%	6	13.6%	22	7.9%	

**Legend.** Data are n (%), median (range) and mean ( $\pm$ SD), \* skewed distribution, Mann-Whitney test applied.

**Figure 1.** Inclusion flowchart

## RLNP

In the McKeown group, 44 of the 324 patients (14%) were found to have a postoperative RLNP (the RLNP+ group). Interestingly, in the cohort of transhiatal esophagectomies RLNP occurred in only 3/127 (2%) patients.

In our study population of McKeown esophagectomies: 33/44 RLNPs were diagnosed through laryngoscopy, 11/44 RLNP patients were diagnosed by clinical examination (Table 2). Most patients (29/44) presented with a left RLNP, 3/44 had a right RLNP, 8/44 had bilateral palsy, and for 4/44 patients the location was unknown. The majority of patients were diagnosed with a paresis (27/44); the most common symptoms at presentation were dysphonia (43/44) and/or aspiration (25/44). Of all patients diagnosed with RLNP, the majority (36/44) received speech and language therapy (SLT), 21/44 were kept nil-per-os (NPO). Lymph node yield was higher in the RLNP+ group (24.5 (7-57) versus 22 (6-53) in the RLNP- group,  $p < 0.001$ ). There was also a significant difference in the pathological T-stage between the two groups ( $p=0.044$ ), with more T3-T4 tumors in the RLNP+ group and more T0-T2 tumors in the RLNP- group, as is shown in Table 1.

**Table 2.** Recurrent Laryngeal Nerve Palsy characteristics and treatment

Characteristics		RLNP+ (N=44)
		n (%)
Location	Left	29 (65.9%)
	Right	3 (6.8%)
	Bilateral	8 (18.2%)
	Unknown	4 (9.1%)
Palsy	Paresis	27 (61.4%)
	Paralysis	16 (36.4%)
	Unknown	1 (2.3%)
ENT consultation	Yes	30 (68.2%)
	No	14 (31.8%)
Clinical presentation	Dysphonia	43 (97.7%)
	Aspiration	25 (56.8%)
Diagnostics	Clinical	11 (25.0%)
	Laryngoscopy	33 (75.0%)

**Table 2 continued.** Recurrent Laryngeal Nerve Palsy characteristics and treatment

Characteristics		RLNP+ (N=44)
Therapy	NPO	21 (47.7%)
	SLT	36 (81.8%)
	Thyroplasty	6 (13.6%)
Recovery	Yes	10 (22.7%)
	No	5 (11.4%)
	Partially	6 (13.6%)
	less than 6 months follow-up	23 (52.3%)

**Legend.** Data are n (%).

**Abbreviations.** ENT: ear nose throat specialist, SLT: speech and language therapy, NPO: nil per os.

### Postoperative outcomes

In the univariable analysis, there were significantly more postoperative pulmonary complications in the RLNP+ group (61% versus 41% in the RLNP- group;  $p=0.013$ ) (Table 3). Specifically, there was a significantly higher amount of atelectasis (34% versus 9%;  $p<0.001$ ) and tracheostomies performed (16% versus 6%;  $p=0.014$ ) in the RLNP+ group. The difference in length of hospital stay between the RLNP+ and RLNP- groups was not statistically significant (19 versus 15 days, respectively;  $p=0.084$ ).

**Table 3.** Postoperative complications

Outcomes		RLNP+ (N=44)		RLNP- (N=280)		<i>p</i> value
		n	%	n	%	
<b>Pulmonary complications</b>	Total	27	61.4%	116	41.4%	0.013
	Pneumonia	21	47.7%	106	37.9%	0.213
	Atelectasis	15	34.1%	25	8.9%	<0.001
	Tracheostoma	7	15.9%	16	5.7%	0.014
<b>Reintervention</b>		18	40.9%	93	33.2%	0.317
<b>30- d postoperative mortality</b>		0	0.0%	16	5.7%	0.104
<b>ICU stay (days)*</b>		1	(1-43)	1	(1-155)	0.620
<b>Hospital stay (days)*</b>		19	(9-80)	15	(3-182)	0.084
<b>Readmission</b>		5	11.4%	28	10.0%	0.787

**Legend.** Data are n (%) \* skewed distribution, Mann-Whitney test applied.

**Abbreviations.** ICU: Intensive care unit.

Results from the multivariable analyses are shown in Table 4 and 5. RLNP was associated with a higher incidence of pulmonary complications (Table 4) (OR 2.391; 95% CI 1.222-4.679;  $p=0.011$ ). In addition, diabetic comorbidity was also associated with a higher incidence of pulmonary complications (OR 2.126; 95% CI 1.050-4.304;  $p=0.036$ ). Moreover, RLNP was associated with a prolonged hospital stay (+4 days) ( $p=0.001$ , table 5). Other factors associated with a longer hospital stay were older age (above 65 years) ( $p=0.039$ ), pulmonary comorbidity ( $p=0.005$ ), diabetes mellitus ( $p=0.008$ ), anastomotic leakage ( $p < 0.001$ ), chylothorax ( $p<0.001$ ). Factors associated with a shorter hospital stay were the ability to receive neoadjuvant chemotherapy ( $p=0.017$ ) or chemoradiotherapy ( $p=0.002$ ).

**Table 4.** Pulmonary complications: univariable and multivariable analysis

	Univariable			Multivariable		
	OR	[95% CI]	p-value	OR	[95% CI]	p-value
<b>Female gender</b>	0.771	[0.471-1.261]	0.301			
<b>Age</b>	0.993	[0.968-1.019]	0.614	0.991	[0.964-1.019]	0.525
<b>BMI</b>	1.020	[0.970-1.072]	0.441			
<b>ASA score</b>						
I	Ref	-	-			
II	1.065	[0.635-1.788]	0.811			
III	1.371	[0.651-2.890]	0.406			
<b>Pulmonary comorbidity</b>	1.325	[0.731-2.400]	0.354	1.462	[0.786-2.718]	0.230
<b>Cardiac comorbidity</b>	1.293	[0.750-2.230]	0.356			
<b>Vascular comorbidity</b>	0.871	[0.519-1.462]	0.602			
<b>Diabetes mellitus</b>	2.080	[1.059-4.085]	0.033	2.126	[1.050-4.304]	0.036
<b>Neoadjuvant treatment</b>						
None	Ref	-	-	Ref	-	-
Chemotherapy	0.787	[0.437-1.417]	0.425	0.738	[0.401-1.356]	0.327
Chemoradiotherapy	0.709	[0.421-1.194]	0.196	0.660	[0.380-1.144]	0.139
<b>Minimally invasive surgery</b>	0.966	[0.546-1.711]	0.907	0.853	[0.463-1.572]	0.611
<b>Prox tumor location*</b>	0.747	[0.428-1.303]	0.304			
<b>pT3-4 stage</b>	1.157	[0.744-1.798]	0.518			

**Table 4 continued.** Pulmonary complications: univariable and multivariable analysis

	Univariable		Multivariable			
pN+ stage	0.977	[0.629-1.515]	0.916			
Lymph node yield	0.980	[0.959-1.002]	0.076	0.982	[0.959-1.005]	0.119
Irradical resection **	1.295	[0.596-2.812]	0.514			
Anastomotic leakage	0.842	[0.494-1.436]	0.528			
Chylothorax	1.241	[0.717-2.148]	0.440			
Recurrent nerve paresis	2.245	[1.170-4.309]	0.015	2.391	[1.222-4.679]	0.011

*Legend.* \* Tumor of the proximal or middle esophagus, \*\* R1 or R2 resection.

*Abbreviations.* ASA: American Society of Anesthesiologists, BMI: Body Mass Index.

**Table 5.** Hospital stay (no IHM): univariable and multivariable analysis

	Multivariable			
	B*	[95% CI]	Additional days	p-value
Female gender	0.059	[-0.059;0.176]	1	0.329
Age >65 years	0.114	[0.006;0.222]	2	0.039
BMI >25 kg/m <sup>2</sup>	0.071	[-0.037;0.180]	1	0.198
ASA score				
I	Ref	-		-
II	0.043	[-0.085;0.172]	1	0.510
III	-0.017	[-0.207;0.172]	0	0.859
Pulmonary comorbidity	0.215	[0.066;0.363]	4	0.005
Cardiac comorbidity	0.078	[-0.062;0.218]	1	0.277
Vascular comorbidity	-0.008	[-0.147;0.132]	0	0.916
Diabetes mellitus	0.227	[0.058;0.396]	4	0.008
Neoadjuvant treatment				
None	Ref	-		-
Chemotherapy	-0.174	[-0.317;-0.310]	-2	0.017
Chemoradiotherapy	-0.218	[-0.354;-0.083]	-3	0.002
Minimally invasive surgery	-0.120	[-0.261;0.021]	-2	0.095
Anastomotic leakage	0.614	[0.483;0.744]	13	<0.001
Chylothorax	0.389	[0.255;0.523]	7	<0.001
Recurrent nerve paresis	0.250	[0.096;0.403]	4	0.001

*Legend.* \* Intercept = 2,708 (15 days)

*Abbreviations.* ASA: American Society of Anesthesiologists, BMI: Body Mass Index.

**Functional outcomes**

The RLNP+ group is further characterized in Table 2. For functional outcome analysis only patients with a follow-up of at least 6 months were included (n=21). Median follow-up was 17.5 months (7-135). During follow-up, almost half of patients made a full recovery (10/21), 5/21 patients recovered partially, and 6/21 patients did not recover. For 6/21 of these patients surgical intervention (medialization thyreoplasty) was required. All treatment interventions for vocal cord paralysis were conducted after a median time of 16.5 months (11-29) after esophagectomy. Of all patients that underwent medialization thyreoplasty, 3/6 had no more RLNP symptoms afterwards 2/6 made a partial recovery from their RLNP, and 1/6 did not recover.



## Discussion

The present study demonstrates that RLNP after esophagectomy was an independent predictor for both pulmonary complications and increased hospital stay. Moreover, it shows that over half of patients with RLNP after esophagectomy did not fully recover during follow-up, and a substantial part (14%) needed a surgical intervention to recover from RLNP.

These results stress the importance of preserving the RLN for both short- and long-term outcomes, since several studies have demonstrated that pulmonary complications significantly increase the ICU readmission rate, length of hospital stay and mortality rate, and permanent RLNP after esophagectomy deteriorates quality of life.<sup>15,28,29</sup>

Similar to other Western studies reporting on RLNP after McKeown esophagectomy with a two-field lymph node dissection and cervical anastomosis, this study found a RLNP incidence of 14%. Nevertheless, most RLNPs were temporary, indicating that injury of the RLN is rather caused by indirect actions like compression or traction of the nerve than direct damage. Asian studies report RLNP incidences up to 59%.<sup>8,9,13,16</sup> This is mainly attributed to the extensive three-field lymph node dissection which is standard of care in Asia. Notably, our data also showed that patients with RLNP had a significantly higher lymph node yield, possibly indicating a more extensive lymph node dissection in these patients. Also, in this series, in the three stage procedures, a level 2 and 4 (paratracheal) lymph node dissection was always performed.

The results of this study regarding short-term complications after RLN injury during esophagectomy are in line with current literature.<sup>9,10,20,23,24</sup> The first study published on this topic found higher rates of pulmonary complications after RLNP, leading to a higher reintubation rate, and consequently a prolonged ventilation time and longer ICU stay.<sup>23</sup>

These findings were confirmed in more recent studies, all demonstrating an increase in pulmonary complications after esophagectomy complicated by RLNP.<sup>9,10,20,24</sup> Similarly to our results, Koyanagi et al.<sup>10</sup> found an association between RLNP and prolonged hospital stay. No other studies could confirm this finding, though these studies were limited by their small sample sizes.

This study demonstrates that preventing RLNP during esophagectomy is not only pivotal for improving short-term, but also long-term surgical outcomes. The only study in which results regarding RLNP recovery after esophagectomy are published to date focused on quality of life 1 year after RLNP and found a significant deteriorated quality of life after permanent nerve paralysis due to esophagectomy.<sup>12</sup> Hence, precautions to prevent RLNP can improve the outcomes after esophagectomy.

Considering its harmful consequences, it is important to find ways to prevent RLNP during esophagectomy. After transhiatal esophagectomy the RLNP incidence was 2%, while this was 14% after McKeown esophagectomy. This indicates that the RLN is at risk during high mediastinal lymph node dissection. In accordance with current literature, the majority of patients in the present study were diagnosed with a left-sided palsy.<sup>10,20</sup> The left RLN is longer than the right RLN and is situated close to lymph node stations 2L and 4L, consequently being more at risk for injury during lymph node dissection. Meticulous dissection of these stations is pivotal since there is a high frequency of lymph node metastasis.<sup>30–32</sup> We experience robotic assistance of great value to perform a full paratracheal lymph node clearance, which was the standard of care for all these patients.<sup>33,34</sup> Robotic assistance facilitates meticulous dissection along the left RLN and may reduce the incidence of RLNP.<sup>14,35</sup>

Surgically induced RLNP is often not recognized during the procedure. Noninvasive intraoperative neurological monitoring (IONM) may enable surgeons to identify and preserve the RLN. IONM is already widely used in thyroid surgery, and although its effectiveness for esophagectomy is not well recognized, several studies report lower RLNP and consequently lower pulmonary complication rates.<sup>8,20,36–38</sup> Therefore, the use of IONM may be considered for esophagectomy, particularly during high mediastinal lymph node dissection.<sup>10</sup> A substantial part of RLNP is due to thermal injury. Electrocautery devices are used for hemostasis around the RLN during esophagectomy and may deliver heat at a single temperature or a range of temperatures, between 100°C and 1200°C. The use of alternatives to an electrocautery device, reducing maximum temperatures may be another measure to reduce RLNP rates.<sup>39</sup> Additionally, the use of an intrathoracic anastomosis instead of a cervical anastomosis may also reduce the incidence of RLNP after esophagectomy,<sup>20,21</sup> most probably because of

the fact that the upper mediastinum is not fully dissected in these cases.

Besides avoiding unnecessary RLNP, early diagnosis might prevent complications secondary to RLNP. Over half of patients in the current study were diagnosed with RLNP after clinical presentation with symptoms of aspiration. In case of early diagnosis, one may decide to properly evaluate the swallowing process and potentially postpone oral intake, reducing aspiration pneumonia rates.<sup>20</sup>

The majority of patients underwent speech and language therapy after hospital discharge, resulting in a satisfactory function of voice and swallowing. However, due to persistent symptoms, 14% of all RLNP patients needed secondary surgery (medialization thyroplasty), leading to a full or partial recovery in 5 out of 6 patients. All procedures were conducted in the absence of spontaneous recovery  $\geq 10$  months after esophagectomy. This suggests that these patients may have benefited from earlier intervention, since several studies on early versus late medialization show favorable outcomes for patients in early cohorts.<sup>40,41</sup>

Strengths of this study include its large sample size from a prospective database of Western patients and the detailed information on both short- and long-term outcomes available from the database. Despite this, certain limitations apply to the current analysis. It was not possible to obtain data on recovery in all patients. All patients in which follow-up data was missing had early recurrent disease. This made complaints regarding RLNP of minor importance, resulting in poor registration. Lastly, an unexpected lower rate of cardiac comorbidity was found in the RLNP+ group. Although multivariable analysis corrected for all known confounders such as cardiac comorbidity, there may have been other unexpected, unknown confounders which were not included in the analysis, which may have led to bias.

The present study shows that RLNP after esophagectomy is associated with an increased pulmonary complication rate, longer hospital stay, and a moderate long-term recovery. This warrants further studies examining technologies that may reduce RLNP rates.

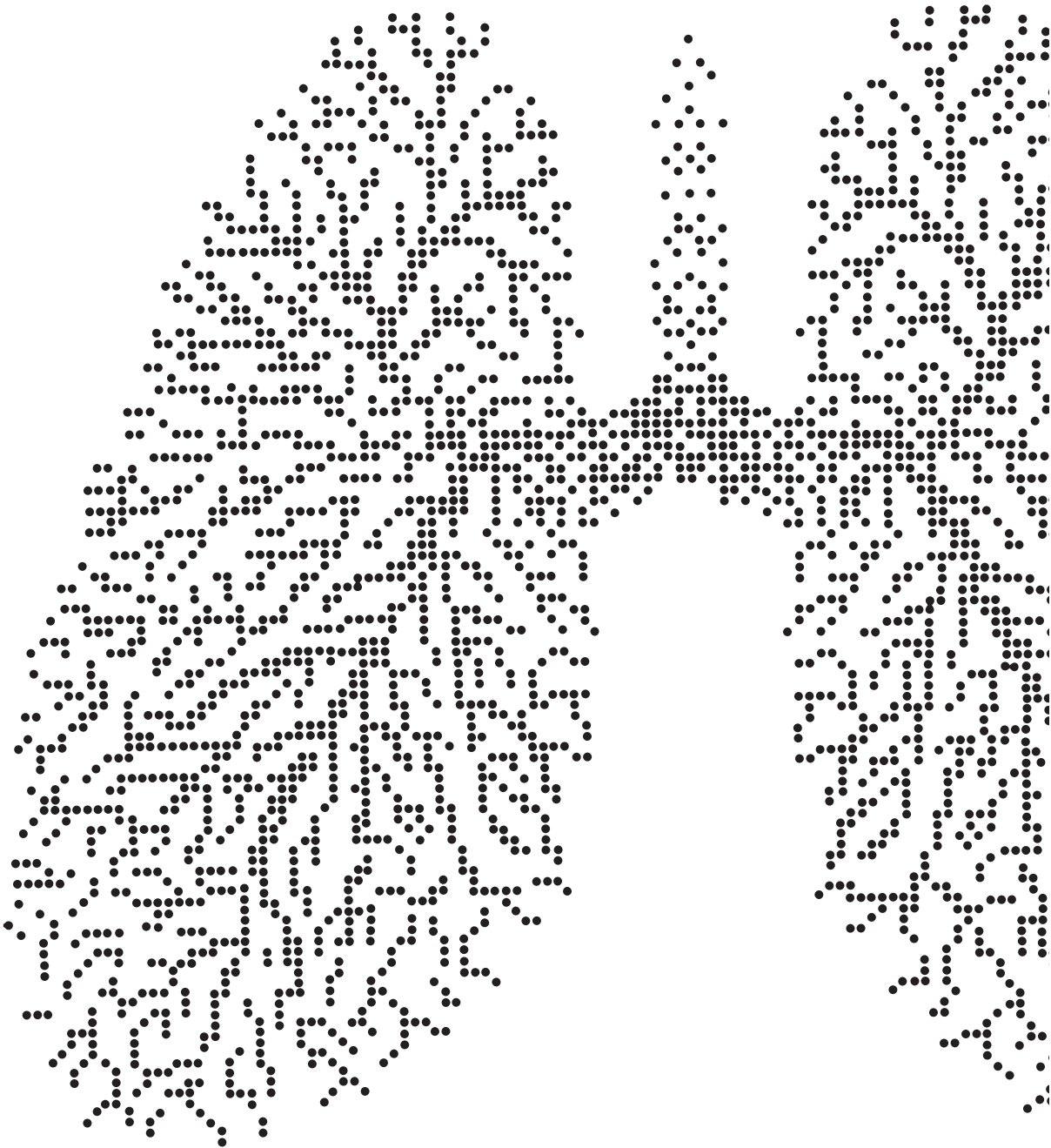
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# Chapter 8

The predictive value  
of new-onset atrial  
fibrillation on  
postoperative morbidity  
after esophagectomy  
for cancer

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## Abstract

**Background:** New-onset atrial fibrillation (AF) is frequently observed following esophagectomy and may predict other complications. The aim of the current study was to determine the association between new-onset AF and infectious complications following esophagectomy.

**Materials & Methods:** Consecutive patients who underwent elective esophagectomy with curative intent for esophageal cancer between 2004 and 2016 in the University Medical Center Utrecht were included, from a prospective database. The date of diagnosis of the complications included in the current analysis was retrospectively collected from the computerized medical record. The association between new-onset AF and infectious complications was studied in univariable and multivariable logistic regression analyses.

**Results:** A total of 455 patients were included. In 93 (20.4%) patients new-onset AF was encountered after esophagectomy. There were no significant differences in patient and treatment-related characteristics between the patients with and without AF. In 9 (9.7%) patients, AF was the only adverse event following surgery. In multivariable analyses, AF was significantly associated with infectious complications in general (OR 3.00, 95% CI: 1.73-5.21). More specifically, AF was associated with pulmonary complications (OR 2.06, 95% CI: 1.29-3.30), pneumonia (OR 2.41, 95% CI: 1.48-3.91) and anastomotic leakage (OR 3.00, 95% CI: 1.80-4.99).

**Conclusion:** In patients that underwent esophagectomy, new-onset AF was highly associated with infectious complications. AF may serve as an early clinical warning sign for anastomotic leakage. Therefore, further evaluation of patients who develop new-onset AF after esophagectomy is warranted.

## Introduction

Curative treatment for patients with resectable locally advanced esophageal cancer consists of neoadjuvant chemoradiotherapy followed by esophagectomy with en-bloc lymphadenectomy.<sup>1,2</sup> Although mortality following esophagectomy steadily decreased over the past years, morbidity rates remain high compared to other elective cancer surgery.<sup>1,3,4</sup> The most frequently encountered postoperative complications include pulmonary complications (12-46%), anastomotic leakage (0-35%), and atrial fibrillation (AF) (12-37%).<sup>1,5-10</sup>

AF increases the risk of embolic events and hemodynamic instability, potentially resulting in organ hypoperfusion.<sup>11</sup> Although the exact pathophysiology of new-onset AF after esophagectomy remains unclear, several retrospective studies demonstrated a significant association between new-onset AF and other postoperative complications.<sup>6, 8, 10</sup> Therefore, it was hypothesized that AF could be of clinical predictive value if AF was shown to precede other postoperative complications. Although the most recent and largest study published to date confirms the association between new-onset AF after esophagectomy and pulmonary complications, it did not demonstrate a significant relation between AF and anastomotic leakage.<sup>11</sup>

The aim of the current study was to determine the association between, and the possible predictive value of, new-onset AF and infectious complications following esophagectomy, with a focus on the 2 most frequently encountered complications after esophagectomy, namely pulmonary complications and anastomotic leakage.

## Materials & Methods

### Patients

Consecutive patients who underwent an elective esophagectomy for esophageal or gastro-esophageal junction cancer with curative intent between 2004 and 2016 at the University Medical Center (UMC) Utrecht were included in this study. Exclusion criteria included preoperative presence of AF and American Association of Anaesthesiologists (ASA) IV classification. Patients included in the current study were not given routine AF prophylaxis postoperatively.

Patient and treatment-related characteristics, as well as surgical outcome data were prospectively recorded in an Institutional Review Board (IRB) approved database. The date of diagnosis of the complications included in the current analysis was retrospectively collected from the computerized medical record. C-Reactive Protein (CRP) levels were registered at the day of AF diagnosis. This study was approved by the Medical Ethics Review Committee of the UMC Utrecht (IRB-number 13-061/C), and informed consent was waived.

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### Surgical approach

The standard surgical approach for esophageal cancer at the UMC Utrecht was a transthoracic robot assisted minimally invasive esophagectomy. However, some patients underwent an open transthoracic esophagectomy, since they were included in the ROBOT trial.<sup>12</sup> When a patient was considered to be too frail to be eligible for a transthoracic approach, a (minimally invasive) transhiatal esophagectomy was performed. In all hybrid procedures the thoracic phase was conducted in a robot assisted minimally invasive manner and the abdominal phase was conducted in an open manner due to contraindications for laparoscopic surgery. After resection, all patients underwent a gastric conduit reconstruction (using a posterior mediastinal route). Subsequently, a bilateral thoracic drain was placed. A cervical anastomotic drain was not routinely placed. After surgery, if no pneumothorax occurred, and drain production was less than 200 ml/24 hours the thoracic drains were removed.

### Fluid management

Fluid strategy was aimed at a mildly positive fluid balance of ~500 ml at the end of the operative procedure. The perfusion status of patients was constantly monitored based on the urine

production, mean arterial pressure, and fluid balance. Postoperatively, when mean arterial pressure was below 65 mmHg, or a urine production of less than 0.5 mL/kg/hour volume loading and/or epinephrine administration was initiated. Crystalloids, and/or epinephrine was administered in case of hypoperfusion. However, since excessive fluid administration is a risk factor for the development of respiratory complications after esophageal surgery, this was performed to a limited extent.

### Outcomes

New-onset AF was diagnosed and documented by means of electrocardiography. Standard treatment for AF included amiodarone, digoxin,  $\beta$ -blockade or a combination. Overall infectious complications included pulmonary infections, anastomotic leakage, mediastinitis, thoracic empyema, sepsis, bowel ischemia, abscesses, central line infection, thrombophlebitis, wound infections, urinary tract infections, pericarditis and endocarditis. Pneumonia was defined by the Uniform Pneumonia Score.<sup>13, 14</sup>

Other pulmonary complications included pleural effusion requiring drainage, pneumothorax requiring treatment, respiratory failure requiring reintubation, acute respiratory distress syndrome and pleural empyema.<sup>15</sup> Anastomotic leakage was defined as a gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit, irrespective of presentation or method of identification.<sup>15</sup>

### Statistical analyses

The association between patient and treatment-related characteristics and new-onset AF was studied univariably. Depending on the cell count, the chi-square or Fisher's exact test was used for categorical variables (i.e. a cell count  $\leq 5$ ). The independent samples t-test or Mann-Whitney U test were used for normally or skewed distributed continuous variables, respectively. All continuous data were presented as mean ( $\pm$  standard deviation) or median (interquartile range) and categorical data were presented as number (percentage).

The association between new-onset AF and other infectious complications was studied in an univariable and multivariable logistic regression model. Variables to be entered into the multivariable logistic regression model along with new-onset AF were based on clinical rea-

soning and literature review as well as univariable analysis, to be able to assess whether new-onset AF was independently and significantly associated with the occurrence of these infectious complications. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and Wald test statistic p-values were calculated. Furthermore, the time interval between day of AF diagnosis and other complications was analysed. Statistical analysis was performed using SPSS version 21.0 software (IBM Corp., Armonk, NY). P-values < 0.05 were considered statistically significant.

## Results

### Patients

Among 479 patients that underwent esophagectomy for esophageal or gastroesophageal junction cancer with curative intent, 24 patients were excluded. (Figure 1) Patient and treatment-related characteristics of the final study population of 455 patients are shown in Table 1.

**Table 1.** Patient and treatment-related characteristics and their univariable association with the occurrence of new-onset atrial fibrillation after esophagectomy

Characteristic		AF (N = 93)	No AF(N = 362)	P
		N (%)	N (%)	
<b>Sex</b>	Female	67 (20.0)	268 (80.0)	0.698
	Male	26 (21.7)	94 (78.3)	
<b>Age, years (mean <math>\pm</math> SD)</b>		65 $\pm$ 8	63 $\pm$ 9	0.084
<b>BMI, kg/m<sup>2</sup> ( mean <math>\pm</math> SD)</b>		25 $\pm$ 4	26 $\pm$ 4	0.663
<b>ASA classification</b>	I	17 (18.3)	91 (25.1)	0.242
	II	60 (64.5)	214 (59.1)	
	III	16 (17.2)	57 (15.7)	
<b>Comorbidities</b>				
	Pulmonary	22 (23.7)	83 (22.9)	0.882
	Cardiac	22 (23.7)	77 (21.3)	0.619
	Vascular	41 (44.1)	125 (34.5)	0.088
	Diabetes mellitus	9 (9.7)	52 (14.4)	0.237
<b>Histology</b>	AC	65 (69.9)	264 (72.9)	0.422
	SCC	22 (23.7)	91 (25.1)	
	Other*	6 (6.5)	7 (1.9)	
<b>(y)pT stage</b>	T0	16 (17.2)	53 (14.6)	0.978
	T1	11 (11.8)	62 (17.1)	
	T2	16 (17.2)	46 (12.7)	
	T3	43 (46.2)	182 (50.3)	
	T4	6 (6.5)	17 (4.7)	
	In situ	1 (1.1)	2 (0.6)	
<b>(y)pN stage</b>	N0	53(57.0)	161 (44.5)	0.167
	N1	16 (17.2)	100 (27.6)	
	N2	11 (11.8)	68 (18.8)	
	N3	13 (14.0)	33 (9.1)	

**Table 1 continued.** Patient and treatment-related characteristics and their univariable association with the occurrence of new-onset atrial fibrillation after esophagectomy

Characteristic		AF (N = 93)	No AF(N = 362)	P
<b>Location of tumor</b>	Cervical	2 (2.2)	3 (0.8)	0.320
	Proximal	4 (4.3)	9 (2.5)	
	Middle	9 (9.7)	54 (14.9)	
	Distal	40 (43.0)	119 (32.9)	
	GEJ	38 (40.9)	177 (48.9)	
<b>Neoadjuvant treatment</b>	No	30 (32.3)	137 (37.8)	0.225
	Chemotherapy	25 (26.9)	99 (27.3)	
	Radiotherapy	0 (0)	1 (0.3)	
	Chemoradiotherapy	38 (40.9)	125 (34.5)	
<b>Surgical approach</b>	TT RAMIE	49 (52.7)	216 (59.7)	0.075
	TT OE	18 (19.4)	39 (10.8)	
	TH MIE	12 (12.9)	65 (18.0)	
	TH OE	12 (12.9)	35 (9.7)	
	Hybrid	2 (2.2)	7 (1.9)	
<b>Location of anastomosis</b>	Cervical	91 (97.8)	358 (98.9)	0.431
	Intrathoracic	2 (2.2)	4 (1.1)	
<b>Duration of surgery, min* (mean, <math>\pm</math> SD)</b>		363 $\pm$ 101	368 $\pm$ 94	0.663
<b>Intra-operative bloodloss, ml<sup>o</sup> (median, IQR)</b>		370 (370)	320 (450)	0.366

**Legend.** Data are n (%), median (IQR) and mean ( $\pm$ SD).

**Abbreviations.** AC = adeno carcinoma, AF = atrial fibrillation, ASA= American Society of Anesthesiologists. BMI = Body Mass Index, GEJ = gastroesophageal junction, Hybrid = thoracic phase RAMIE, abdominal phase open, OE = open esophagectomy, RAMIE = robot assisted minimally invasive esophagectomy, SCC = squamous cell carcinoma, TH = transhiatal, TT = transthoracic.

\*carcinoma in situ, gastrointestinal stromal tumor, basaloid squamous cell carcinoma or undifferentiated tumor cells.

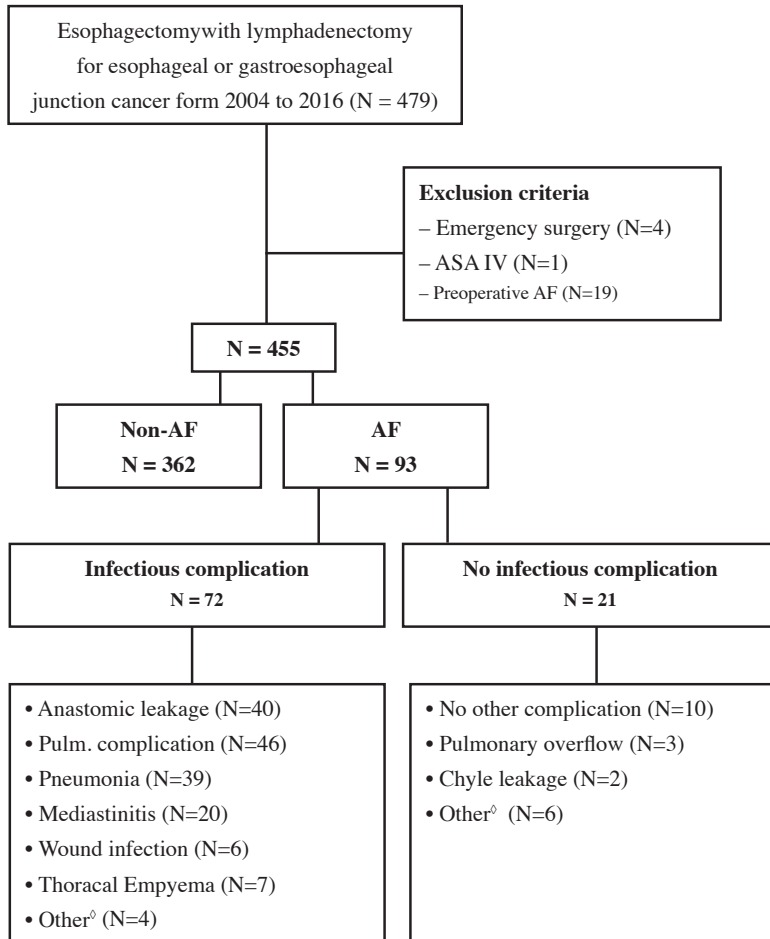
\* Value was based on 428 cases

<sup>o</sup> Value was based on 424 cases

New-onset AF occurred in 93 (20.4%) patients. No significant differences in patient and treatment-related characteristics between patients with and without AF were observed. The median age (range) of the patients was 65 years (34-84), with 60.0% (274) of patients having an ASA II status. Most patients (329, 72.3%) had an adenocarcinoma. The majority of patients had a distal (159, 34.9%) pT3 (225, 49.5%), pN0 (214, 47.0%) tumor. Robot assisted minimally invasive esophagectomy (RAMIE) was performed in 265 (58.2%) patients and in 449 (98.7%) patients



the cervical anastomosis was hand-sewn.



**Figure 1.** Flowchart.

**Legend.** Other = pericarditis, endocarditis, recurrent laryngeal nerve palsy, pulmonary embolism or hypotension

**Abbreviations:** AF = Atrial Fibrillation, ASA = American Society of Anesthesiologists.

### Postoperative outcomes

The majority of postoperative infectious complications were more frequently observed in patients with AF versus patients without AF: overall infectious complications 77.4% vs. 53.6% ( $P < 0.001$ ), pulmonary complications (pooled) 49.5% vs. 33.4% ( $P = 0.004$ ), pneumonia 41.9% vs. 23.5% ( $P < 0.001$ ) and anastomotic leakage 43.0% vs. 21.3% ( $P < 0.001$ ).

Chyle leakage rates did not significantly differ between both groups: 22.6% (AF) vs. 17.4% (non-AF) ( $P = 0.251$ ). In addition, in-hospital or 30-day mortality was significantly higher in patients with AF: 9.7% (AF) versus (vs.) 3.3% (non-AF) ( $P = 0.009$ ). (Table 2) Median (interquartile range [IQR]) hospital stay was 23 days (15-37) in patients with AF and 15 days (12-22) in patients without AF ( $P < 0.001$ ). Also median (IQR) intensive care unit stay was significantly increased in patients with AF (3 days (1-10)) when compared to patients without AF (1 day (1-3)) ( $P < 0.001$ ).

**Table 2.** Morbidity and mortality in patients with and without new-onset atrial fibrillation (AF) following esophagectomy

Characteristic	AF (N = 93)	No AF (N = 362)	P
	N (%)	N (%)	
<b>In-hospital or 30-day mortality, days</b>	9 (9.7)	12 (3.3)	0.009
<b>Hospital stay, days (median, IQR)</b>	23 (15-37)	15 (12-22)	<0.001
<b>ICU stay, days (median, IQR)</b>	3 (1-10)	1 (1-3)	<0.001
<b>Any postoperative complication</b>	N/A	243 (67.1)	N/A
<b>Reintervention</b>	35 (44.3)	80 (26.5)	0.002
<b>Surgical complications</b>	60 (64.5)	170 (47.0)	0.003
<b>Infectious complications</b>	72 (77.4)	194 (53.6)	<0.001
<b>Pneumonia</b>	39 (41.9)	85 (23.5)	<0.001
<b>Pulmonary embolus</b>	10 (10.8)	9 (2.5)	<0.001
<b>Any pulmonary complications</b>	46 (49.5)	121 (33.4)	0.004
<b>Anastomotic leak/conduit necrosis</b>	40 (43.0)	77 (21.3)	<0.001
<b>Chyle leak</b>	21 (22.6)	63 (17.4)	0.251
<b>Myocardial infarction</b>	0 (0)	3 (0.8)	0.378

**Legend.** Data are n (%) and median (IQR).

**Abbreviations.** AF = atrial fibrillation, ICU = Intensive Care Unit.

Median (range) time to development of AF after surgery was 3.0 (0-38) days. As shown in figure 1, 84 (90.3%) of the patients with new-onset AF developed a second complication. In univariable analysis, new-onset AF was significantly associated with infectious complications (OR 2.97, 95% CI: 1.75-5.04] (Table 3a). More specifically, new-onset AF was also

associated with pulmonary complications (OR 1.95, 95% CI: 1.23-3.09; Table 3b), pneumonia (OR 2.35, 95% CI: 1.46-3.80; Table 3c) and anastomotic leakage (OR 2.79, 95% CI: 1.73-4.52; Table 3d).

**Table 3a.** Results of univariable and multivariable logistic regression analysis for infectious complications following esophagectomy

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.02	0.99-1.04	0.103	1.01	0.99-1.04	0.250
ASA	I	reference			reference		
	II	0.89	0.57-1.40	0.612	0.72	0.44-1.17	0.183
	III	1.66	0.88-3.11	0.116	1.35	0.66-2.74	0.410
BMI		1.04	0.99-1.09	0.056	1.06	1.01-1.12	0.017
Preoperative vascular comorbidity		1.04	0.70-1.53	0.850		Not included	
Preoperative cardiac comorbidity		1.18	0.75-1.87	0.472		Not included	
Preoperative diabetes mellitus		1.30	0.75-2.28	0.352	1.16	0.62-2.14	0.647
Preoperative pulmonary comorbidity		1.57	0.99-2.48	0.053	1.69	1.03-2.77	0.039
Neoadjuvant therapy	No	reference					
	Radiotherapy	N=1					
	Chemotherapy	0.73	0.46-1.17	0.193			
	Chemoradiotherapy	1.15	0.74-1.79	0.540		Not included	
Surgical approach	TT RAMIE	reference			reference		
	TT OE	1.66	0.90-3.05	0.102	1.28	0.67-2.43	0.451
	TH MIE	0.97	0.58-1.62	0.906	0.93	0.53-1.62	0.784
	TH OE	0.95	0.51-1.77	0.870	0.88	0.46-1.72	0.715
	Hybrid	6.13	0.76-49.74	0.089	6.17	0.73-52.23	0.095
Intrathoracic anastomosis (versus cervical)		1.43	0.26-7.87	0.683		Not included	
Postoperative chyle leakage		2.15	1.28-3.62	0.004	2.27	1.30-3.96	0.004
Postoperative AF		2.97	1.75-5.04	<0.001	3.00	1.73-5.21	<0.001

**Abbreviations.** AF = atrial fibrillation, ASA= American Society of Anesthesiologists. BMI = Body Mass Index , TT = transthoracic, TH = transhiatal, RAMIE = robot assisted minimally invasive esophagectomy, OE = open esophagectomy, MIE = minimally invasive esophagectomy.

**Table 3b.** Results of univariable and multivariable logistic regression analysis for pulmonary complications following esophagectomy

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.01	0.98-1.03	0.630			
ASA	I	reference			reference		
	II	0.83	0.52-1.31	0.418	0.80	0.50-1.28	0.341
	III	1.43	0.78-2.60	0.249	1.31	0.70-2.44	0.394
BMI		0.99	0.95-1.04	0.772			
Pulmonary comorbidity		1.20	0.77-1.88	0.425	1.17	0.73-1.85	0.516
Recurrent laryngeal nerve damage		2.03	1.10-3.75	0.024	2.11	1.13-3.93	0.019
Postoperative AF		1.95	1.23-3.09	0.005	2.06	1.29-3.30	0.002

*Abbreviations.* AF = Atrial Fibrillation, ASA: American Society of Anesthesiologists, BMI: Body Mass Index

**Table 3c.** Results of univariable and multivariable logistic regression analysis for pneumonia following esophagectomy

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.01	0.98-1.03	0.572		Not included	
ASA	I	reference			reference		
	II	1.07	0.64-1.78	0.798	0.98	0.58-1.66	0.948
	III	1.56	0.82-3.00	0.179	1.35	0.69-2.64	0.389
BMI		1.01	0.97-1.06	0.613		Not included	
Pulmonary comorbidity		1.55	0.97-2.49	0.066	1.51	0.93-2.46	0.095
Recurrent laryngeal nerve damage		1.33	0.69-2.56	0.391	1.44	0.74-2.81	0.283
Postoperative AF		2.35	1.46-3.80	<0.001	2.41	1.48-3.91	<0.001

*Abbreviations.* AF = Atrial Fibrillation ASA: American Society of Anesthesiologists, BMI: Body Mass Index

**Table 3d.** Results of univariable and multivariable logistic regression analysis for anastomotic leakage following esophagectomy

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.02	0.99-1.05	0.092	1.01	0.98-1.04	0.535
ASA	I	reference			reference		
	II	1.13	0.67-1.93	0.645	0.89	0.50-1.58	0.686
	III	1.94	1.00-3.75	0.050	1.39	0.66-2.95	0.390
BMI		1.02	0.97-1.07	0.558		Not included	
Preoperative vascular comorbidity		1.18	0.76-1.81	0.460		Not included	
Preoperative cardiac comorbidity		1.04	0.63-1.72	0.888		Not included	
Preoperative diabetes		1.50	0.84-2.67	0.176	1.46	0.77-2.76	0.390
Preoperative pulmonary comorbidity		1.95	1.22-3.11	0.006	1.81	1.09-3.00	0.021
Neoadjuvant therapy	No	reference					
	Radiotherapy	N=1					
	Chemotherapy	0.83	0.48-1.44	0.503			
						Not included	
	Chemoradiotherapy	1.21	0.74-1.96	0.451			
Surgical approach	TT RAMIE	reference			reference		
	TT OE	0.87	0.44-1.75	0.703	0.70	0.34-1.44	0.329
	TH MIE	1.77	1.02-3.06	0.041	1.78	0.97-3.25	0.062
	TH OE	1.39	0.70-2.76	0.348	1.37	0.66-2.84	0.399
	Hybrid	0.94	0.19-4.62	0.935	0.97	0.18-5.26	0.973
Intrathoracic anastomosis (versus cervical)		1.45	0.26-8.03	0.669		Not included	
Postoperative chyle leakage		1.70	1.02-2.82	0.042	1.89	1.09-3.29	0.024
Postoperative AF		2.79	1.73-4.52	<0.001	3.00	1.80-4.99	<0.001

**Abbreviations.** AF = atrial fibrillation, ASA: American Society of Anesthesiologists, BMI: Body Mass Index, TT = transthoracic, TH = transhiatal, RAMIE = robot assisted minimally invasive esophagectomy, OE = open esophagectomy, MIE = minimally invasive esophagectomy.

New-onset AF remained independently and significantly associated with these complications in multivariable analyses when adjusting for the factors as presented in Table 3 and 4: OR 3.00, 95% CI: 1.73-5.21, for infectious complications, (Table 3a); OR 2.06, 95% CI: 1.29 - 3.30 for pulmonary complications (Table 3b); 2.41, 95% CI: 1.48 - 3.91 for pneumonia (Table 3c) and OR 3.00, 95% CI: 1.80-4.99 for anastomotic leakage (Table 3d). AF either followed pneumonia closely (with a median (range) of 0.5 ( -11 – 25) days) or occurred concurrently.

Contrarily, the diagnosis of anastomotic leakage was preceded by AF with a median (range) of 4.0 (-7.0 – 19) days in patients with AF.

In multivariable analyses within the AF subgroup a significant association was observed between the CRP value at day of AF diagnosis and pneumonia [1.01 (1.00-1.01),  $P = 0.046$ ] (Table 4a), and anastomotic leakage [1.01(1.00-1.01),  $P = 0.011$ ] (Table 4b).

**Table 4a.** Predictive factors for pneumonia in patients with AF (N=93)

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.02	0.97-1.07	0.498		Not included	
ASA	I	reference			reference		
	II	0.38	0.13-1.14	0.083	0.24	0.07-0.83	<b>0.025</b>
	III	0.70	0.18-2.77	0.611	0.48	0.10-2.34	0.369
BMI		1.06	0.96-1.17	0.265		Not included	
Pulmonary comorbidity		0.95	0.36-2.50	0.911	0.65	0.21-1.98	0.448
Recurrent laryngeal nerve damage		0.68	0.18-3.89	0.661		Not included	
CRP at diagnosis AF		1.01	1.00-1.01	0.026	1.01	1.00-1.01	<b>0.046</b>

*Abbreviations:* AF = Atrial Fibrillation ASA = American Society of Anesthesiologists. BMI = Body Mass Index. CRP = C-reactive Protein

**Table 4b.** Predictive factors for anastomotic leakage in patients with AF (N=93)

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Age		1.06	1.00-1.11	0.048	1.06	0.99-1.12	0.054
ASA	I	reference				Not included	
	II	1.50	0.49-4.58	0.477			
	III	1.43	0.35-5.79	0.620			
BMI		0.94	0.85-1.03	0.189		Not included	
Preoperative vascular comorbidity		1.28	0.56-2.91	0.565		Not included	
Preoperative cardiac comorbidity		1.45	0.55-3.78	0.450		Not included	
Preoperative diabetes		1.07	0.28-4.26	0.927		Not included	
Preoperative pulmonary comorbidity		1.84	0.70-4.84	0.214		Not included	

**Table 4b continued.** Predictive factors for anastomotic leakage in patients with AF (N=93)

		Univariable Analysis			Multivariable Analysis		
Variable		OR	95% CI	P	OR	95% CI	P
Neoadjuvant therapy	No	reference			Not included		
	Chemotherapy	1.85	0.62-5.50	0.271			
	Chemoradiotherapy	1.80	0.67-4.85	0.245			
Surgical approach	TT RAMIE	reference					
	TT OE	0.35	0.10-1.22	0.099			
	TH MIE	2.46	0.65-9.24	0.184			
	TH OE	0.88	0.24-3.15	0.840			
	Hybrid	1.23	0.07-20.76	0.887			
Surgical approach OE		0.47	0.19-1.16	0.100	0.41	0.15-1.12	0.082
CRP at diagnosis AF		1.01	1.00-1.01	0.020	1.01	1.00-1.01	0.011

**Abbreviations.** AF = Atrial Fibrillation ASA = American Society of Anesthesiologists. BMI = Body Mass Index, CRP = C-reactive Protein OE = open esophagectomy, MIE = minimally invasive esophagectomy, RAMIE = robot assisted minimally invasive esophagectomy, TH = transhiatal, TT = transthoracic

## Discussion

The current study demonstrates an association between new-onset AF after esophagectomy and postoperative infectious complications in general, and more specifically with pulmonary complications (pooled), pneumonia and anastomotic leakage in a large prospective database from a high volume center. In addition, the time interval between the day of AF diagnosis and the development of anastomotic leakage and pneumonia was studied, revealing the potential predictive value of new-onset AF for anastomotic leakage since the diagnosis of anastomotic leakage is preceded by new-onset AF with a median of 4 days. These findings could aid the early clinical diagnosis and treatment of infectious complications after esophagectomy.

At present, mortality rates in high-volume centers are usually less than 5%.<sup>16-18</sup> However, postoperative complication rates remain relatively high when compared to other elective surgical procedures for cancer. This highlights the importance of further recognizing and reducing complications after esophagectomy for cancer.<sup>1,3,4</sup>

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The incidence of new-onset AF after esophagectomy in the current study was 20.4%, which is in line with previously published studies reporting incidences of 10-37%.<sup>6,8,10,11,19,20</sup> The association between the pre-operative variables age, cardiac comorbidity, and neoadjuvant therapy and AF have been consistent. The current study rather reported on the risk of developing postoperative complications when new-onset AF occurs after surgery, than on variables potentially predicting AF after esophagectomy. Nevertheless, a trend for developing AF after surgery with increasing age could be identified. (Table 1)

This study demonstrated that only 9 (9.7%) out of 93 of patients developing AF after esophagectomy had no other postoperative complications. This is consistent with a recent study by Mc Cormack et al.<sup>11</sup> in which less than 20% of new-onset AF after esophagectomy was seen without other complications. These findings support the hypothesis that AF is associated with other postoperative infectious complications in the majority of cases. However, since that study focussed on associations rather than causal relations, the question remained whether new-onset AF is causative for, or a consequence of other postoperative complications.

During transthoracic esophagectomy, the pleural surfaces and pericardium are exposed. This may lead to direct trauma to the atrium and autonomic nerve fibers, potentially resulting in



AF. In addition, intra-operative single lung ventilation may cause oxidative stress which is linked to AF through mitochondrial dysfunction.<sup>21</sup> AF increases the risk of embolic events and hemodynamic instability, potentially leading to organ hypoperfusion and increasing the likelihood of secondary complications.<sup>11</sup> However, infection may also cause oxidative stress. The diagnosis of pneumonia was concurrent with, or followed the day diagnosis of new-onset AF closely. Previous research by Stawicki et al.<sup>10</sup> reported the same temporal relationship. Due to this relation it may be hypothesized that AF is rather an expression of pulmonary complications than a cause.

The association between AF and anastomotic leakage remains a topic of debate. Although several studies showed a significant association,<sup>6, 8, 10</sup> a recently published study showed no association between AF and anastomotic leakage.<sup>11</sup> The absence of an significant association between AF and anastomotic leakage in the latter study could be explained by the low statistical power of the study, which is reflected by the low number of events (29 cases of anastomotic leakage).

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In another study, 156 patients were studied of which 32 (20.5%) developed new-onset AF after esophagectomy. New-onset AF was significantly associated with anastomotic leakage in univariable analysis, however this association ceased to exist in multivariable analysis.<sup>10</sup> This could be due to a small sample size, rather than to a true absence of an association. Interestingly, the median time between new-onset AF and the clinical diagnosis of anastomotic leakage was 4 days, exactly the same as observed in the current study. This suggests that AF may be a surrogate marker for anastomotic leakage and could therefore be of clinical importance.

To further explore the predictive value of AF for developing other postoperative complications multivariable analyses were conducted within the group of patients who developed AF. (Table 4) The height of serum CRP levels showed to be associated with the development of anastomotic leakage and pneumonia. Therefore increased CRP levels at the day of AF diagnosis is an additional warning sign for the development of postoperative pneumonia and anastomotic leakage in patient with AF.

Several randomized controlled trials have investigated the effect of prophylactic treatment of new-onset AF directly post-esophagectomy.<sup>22-24</sup> All studies reported lower incidences of new-onset AF in the intervention group compared to the placebo group. Only one of these trials reported data regarding postoperative complications. Ojima et al.<sup>22</sup> randomized 100 patients with a 1:1 parallel allocation ratio to either landiolol prophylaxis or placebo. New-onset AF occurred in 15 patients (30%) receiving placebo versus five (10%) receiving Landiolol (P=0.012).

Also Clavien-Dindo grade 2 or higher complications occurred significantly more often in the placebo group (30 (60.0%) vs. 20 (40.0%)). However, pneumonia and anastomotic leakage rates did not differ between groups. The major concern with regard to prophylactic treatment of AF is that it may rather be an early warning sign than causative for anastomotic leakage. Prophylactic treatment for AF may mask an early clinical sign of anastomotic leakage, and potentially delays treatment. Furthermore, AF is relatively easy to treat and resolves fast after treatment initiation.<sup>10, 25, 26</sup> Therefore prevention is not indispensable.

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Certain limitations apply to the current analysis. Some patients had multiple complications after esophagectomy. Therefore, in these patients, one cannot be certain which of these complications was associated with AF. This might have hampered the time interval analyses. Furthermore, it must be noted that a causal relation between AF and infectious complications was not established in the current study. Nevertheless, the current study included a large number of patients from a prospectively kept database and conducted profound statistical analyses.

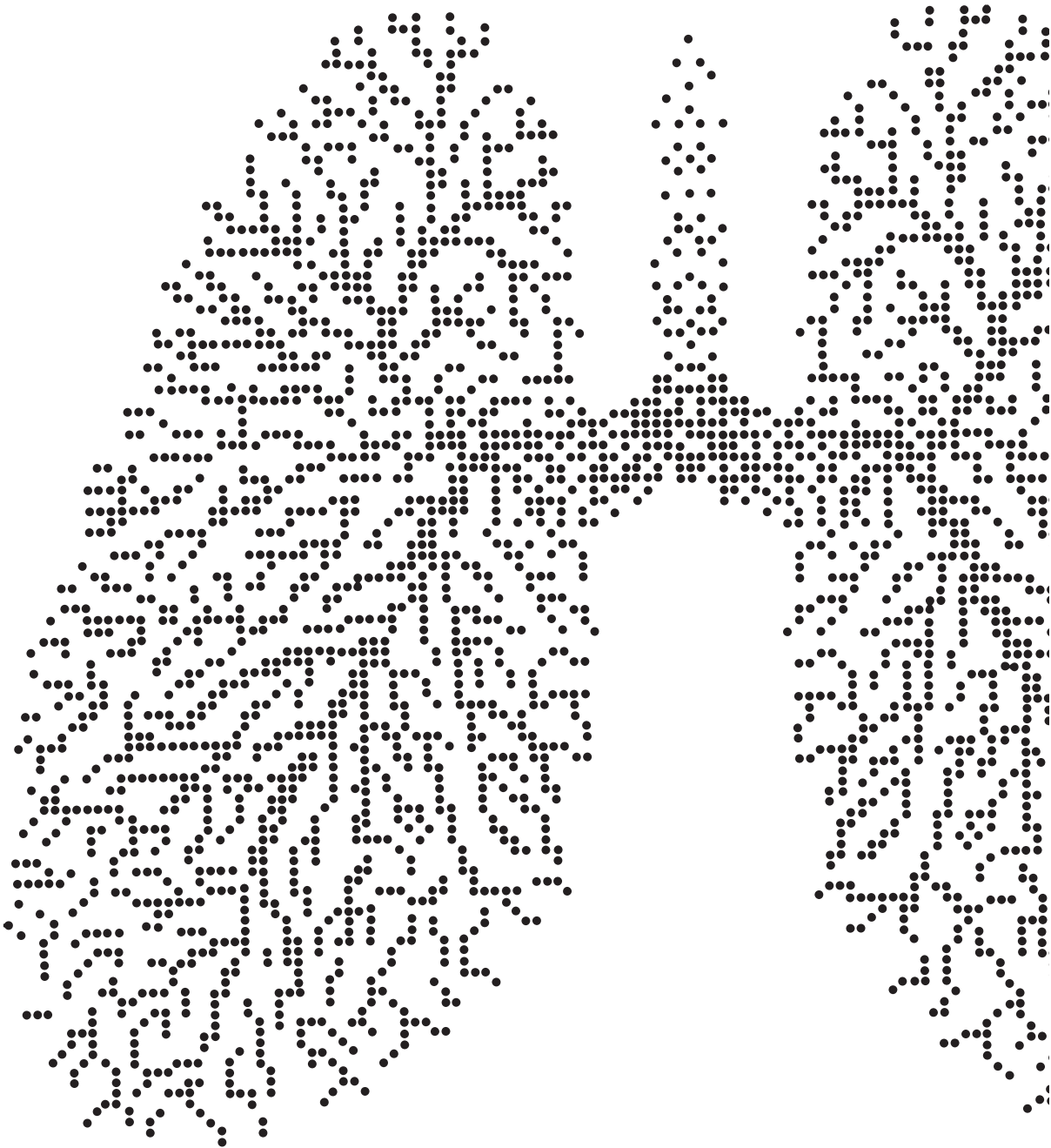
In conclusion, new-onset AF is rarely seen in isolation and it is highly associated with various postoperative infectious complications. It occurs concurrently with pneumonia, but could function as an early clinical warning sign for anastomotic leakage. Therefore it is advocated to thoroughly evaluate patients who develop new-onset AF after esophagectomy for cancer and not only focus treatment on the restoration of sinus rhythm.

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# Chapter 9

## Internal and external validation of a multivariable model to define hospital-acquired pneumonia after esophagectomy

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## Abstract

**Background:** Pneumonia is an important complication following esophagectomy, however a wide range of pneumonia incidence is reported. The lack of one generally accepted definition prevents valid inter-study comparisons. We aimed to simplify and validate an existing scoring model to define pneumonia following esophagectomy.

**Materials & Methods:** The Utrecht Pneumonia Score, comprising of pulmonary radiography findings, leucocyte count and temperature, was simplified and internally validated using bootstrapping in the dataset (n=185) in which it was developed. Subsequently the intercept and (shrunk) coefficients of the developed multivariable logistic regression model were applied to an external dataset (n=201).

**Results:** In the revised Utrecht Pneumonia Score, the Uniform Pneumonia Score (UPS), points are assigned based on: the temperature, the leucocyte count, and the findings on pulmonary radiography. The model discrimination was excellent in the internal validation set and in the external validation set (C-statistics 0.93 and 0.91, respectively), furthermore the model calibrated well in both cohorts.

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**Conclusion:** The UPS can serve as a means to define post-esophagectomy pneumonia. Utilization of a uniform definition for pneumonia will improve inter-study comparability and improve the evaluations of new therapeutic strategies to reduce pneumonia incidence.



## Background

Each year esophageal cancer is diagnosed in 460,000 people worldwide.<sup>1</sup> Esophagectomy is the corner stone of treatment for resectable esophageal cancer. However this complex procedure<sup>2</sup> is associated with a high rate of complications that need an invasive re-intervention(27-38%),<sup>3-6</sup> and a high 90-day mortality rate (approximately 9%).<sup>7</sup> Pulmonary complications are most frequently observed and significantly increase the intensive care unit readmission rate, the length of hospital stay and the mortality rate.<sup>8,9</sup> This stresses the need for strategies to reduce these complications. However, research in pneumonia following esophagectomy -which is the most common postoperative pulmonary complication- is frustrated by the lack of a widely accepted definition that is easy to apply.

The reporting of pneumonia was investigated in a recent systematic review of prospective studies conducted between 2004 and 2009 including more than 50 patients undergoing esophagectomy.<sup>10</sup> Pneumonia rates were reported by 56 studies, but defined by 18 studies only, using 16 different definitions. The variation across reported pneumonia rates was large, ranging from 2-39%.<sup>10</sup> Since the range of pneumonia incidence is so strongly determined by definition, valid inter-study or even within-study comparisons cannot be made.

Recently, an objective scoring system to define pneumonia was developed; the Utrecht Pneumonia Score (Table 1).<sup>8</sup> In this score, pneumonia is defined based on temperature, leucocyte count and pulmonary radiography findings

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This study aims to validate the score both internally and externally.

## Materials & Methods

Approval was obtained from the local medical ethical committee, and the need for informed consent was waived for this study. Analysis and reporting were performed in accordance with the TRIPOD statement.<sup>11</sup> For the internal validation, the original development set of the UPS was used,<sup>8</sup> consisting of a consecutive cohort of patients that underwent an esophagectomy with gastric conduit reconstruction in the University Medical Center Utrecht between October 2003 and March 2011. For the external validation, a cohort of all consecutive patients that underwent an esophagectomy in the Catharina Hospital Eindhoven between January 2008 and March 2014 was used. Data for both cohorts were extracted from prospectively acquired databases which contain patient characteristics and intra- and postoperative data. Model variables had to be collected retrospectively. Exclusion criteria were presence of pneumonia at the time of surgery, and death before model variables could be measured. In addition, complete case analysis was performed by excluding patients with missing values for model variables, as the amount of missing data was low.

**Table 1.** Utrecht Pneumonia Score and Uniform Pneumonia Score, a definition for hospital acquired pneumonia after esophagectomy

	Utrecht Pneumonia Score		Uniform Pneumonia Score	
	Range	Score	Range	Score
Diagnostic determinant Temperature [°C]	≥ 36.1 and ≤ 38.4	0	≥ 36.1 and ≤ 38.4	0
	≥ 38.5 and ≤ 38.9	1	≤ 36.0 and ≥ 38.5	1
	≥ 39.0 and ≤ 36.0	2		
Leukocyte count [x10 <sup>9</sup> /L]	≥ 4.0 and ≤ 11.0	0	≥ 4.0 and ≤ 11.0	0
	< 4.0 or > 11.0	1	< 4.0 or > 11.0	1
Pulmonary radiography	No infiltrate	0	No infiltrate	0
	Diffuse (or patchy) infiltrate	1	Diffuse (or patchy) infiltrate	1
	Well-circumscribed infiltrate	2	Well-circumscribed infiltrate	2

**Legend.** A sum score of 2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography, indicates treatment of pneumonia.

### Surgical procedure and postoperative care

Patients underwent either open or minimally invasive transthoracic or transhiatal esophagectomy with or without robot assistance. Epidural analgesia was administered routinely during

and following surgery. A gastric conduit reconstruction was performed with either a cervical or an intrathoracic anastomosis. Bilateral chest tubes were placed at the end of transthoracic surgery. In the cohort that was used to develop the Utrecht Pneumonia Score a feeding jejunostomy was created in all patients to bridge the nil-by-mouth period in the first 5 to 7 days after esophagectomy. In the validation cohort the same postoperative nutritional regimen was used except for a subset in which the feasibility and safety of direct oral intake following esophagectomy was investigated.<sup>12</sup> All patients were transferred to the intensive care unit postoperatively. When patients were respiratory and hemodynamically stable without support or intensive monitoring they were transferred to the surgical ward.

### Outcome definition

Currently, there is no established well-defined gold standard for diagnosing pneumonia after esophagectomy.<sup>10</sup> Therefore, pneumonia was defined as the clinical decision to treat suspected pneumonia, similarly to van der Sluis *et al.*<sup>8</sup> Treatment for pneumonia, unless contra-indicated, was primarily by intravenous cefuroxime or ceftriaxone.

### Predictors

In accordance with van der Sluis *et al.*<sup>8</sup>, data for the following 3 diagnostic determinants of interest were retrospectively collected from the patients' charts of the medium care unit or hospital ward stay: temperature (°C), leukocyte count ( $\times 10^9/L$ ) and pulmonary radiography findings. Pulmonary radiography findings included chest X-rays and CT scans. In patients not treated for pneumonia, the temperature, leucocyte count and pulmonary radiography were collected on the fourth day at the hospital ward to ensure a sufficient time from ICU discharge. In this study the original Utrecht Pneumonia Score was simplified; the revised Utrecht Pneumonia Score, the Uniform Pneumonia Score (UPS) The same cutoff value's as used by van der Sluis *et al* were applied for pulmonary radiography and leucocyte count (Table 1). In the original model 0, 1 or 2 points could be attributed for temperature. Since the cutoff value for pneumonia is 2 points, with at least 1 point assigned based on pulmonary radiography, it does not matter if 1 or 2 points are assigned for temperature. Thus in the UPS 0 or 1 point could be assigned for temperature ( $\geq 36.1^\circ C$  and  $\leq 38.4^\circ C$ =0 points and  $\leq 36.0^\circ C$  or  $\geq 38.5^\circ C$ =1point).

### Statistical analysis

Data were analyzed using SPSS for windows, version 22.0 (IBM corp., Armonk, New York) and R 3.1.2 open-source software (<http://www.R-project.org>). All continuous data were presented as median (25th percentile-75th percentile), and all categorical data were presented as number (percentage).

Patient and treatment-related characteristics as well as postoperative outcomes besides pneumonia were compared between the development cohort and external cohort to gain insight in potential differences. Continuous data were compared using the Mann-Whitney-U test and categorical data were compared using the chi-square test. Odds Ratios (ORs) along with 95% confidence intervals (CIs) for each variable of the UPS were calculated in the development set.

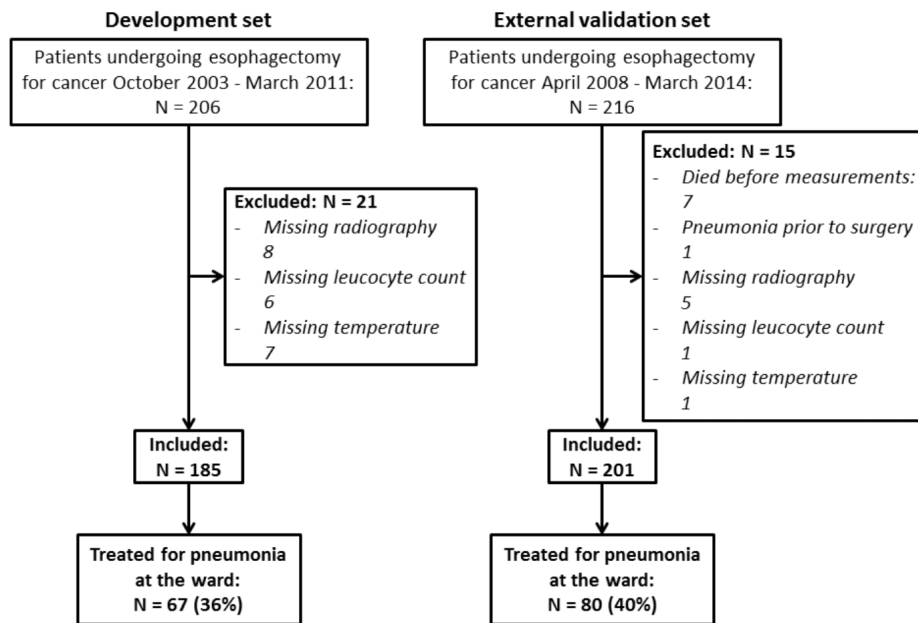
First, the model performance of the UPS was assessed for discriminatory ability and calibration in the development set. The ability to distinguish a patient with the outcome from a patient without the outcome is indicated by discrimination, which was assessed by using the concordance (C) statistic. Calibration refers to the agreement between predicted probability of pneumonia by the model and the observed probability, and was assessed by visual inspection of calibration plots. Second, internal validation of the UPS was performed by applying bootstrap re-sampling with 200 repetitions in the development set. The C-statistics of the original model in the 200 bootstrap samples were averaged, and the optimism was indicated by the differences between this average C-statistic and the original C-statistic.<sup>13</sup>

As such, bootstrapping allowed for adjustment of the model performance for optimism caused by model overfitting, and additionally provided a uniform shrinkage factor that was used to adjust the original model coefficients. Third, the same three variables of the UPS that were included in the internal validation were used for external validation, in which the original intercept and shrunk coefficients after internal validation of the model were applied. Then, external discriminatory ability and calibration were determined.

## Results

### Inclusion

The process of patient selection is shown in Figure 1. For the development dataset 185 patients were included, of who 67 patients (36%) were treated for pneumonia at the ward. The external validation dataset finally consisted of 201 patients of who 80 patients (40%) were treated for pneumonia at the ward.



**Figure 1.** Patient flow

### Patient characteristics

The patient and treatment-related characteristics of the development and validation datasets are presented in Table 2 and 3. Significant differences between both cohorts included the higher rate of ASA 1 patients, T3-T4 tumors, N2-N3 tumors, cervical anastomosis, recurrent nerve injury, lymph nodes resected and a longer hospital admission time among patients in the development set. In the external cohort the rate of alcohol use, neoadjuvant chemoradiation, intrathoracic anastomosis, transhiatal surgery and direct start of oral intake was significantly higher compared to the development cohort.

### Multivariable regression model

The multivariable logistic regression model of the UPS in the prediction of treatment for pneumonia is presented in Table 4. A temperature score of 1 was significantly and independently associated with a higher chance of treatment for pneumonia (OR 12.0,  $p=0.001$ ). A score of 1 for leucocyte count was significantly and independently associated with a higher chance of treatment for pneumonia (OR 6.0,  $p=0.006$ ). Pulmonary radiography findings were significantly and independently associated with an increased chance for pneumonia treatment (1 point: OR 37.4,  $p=0.000$ ; 2 points: OR indefinite).

**Table 2.** Patient characteristics

Variable	Internal validation (n=185)	External validation (n=201)	P-value
<b>Gender</b>			
Male	141 (76)	168 (80)	0.356
Female	44 (24)	40 (19)	
<b>Age</b>	64 (58-71)	64 (57-70)	0.533
<b>Tobacco user</b>	95 (51)	111 (55)*	0.474
<b>Alcohol user</b>	102 (55)	132 (66)*	0.025
<b>Comorbidity</b>			
Cardial	37 (20)	42 (20)	0.327
Diabetes mellitus	26 (14)	23 (11)	0.441
COPD	23 (12)	32 (15)	0.606
<b>ASA score</b>			
I	47 (25)	24 (12)	0.007
II	106 (57)	144 (70)	
III	31 (17)	39 (19)	
IV	1 (<1)	1 (<1)	
<b>BMI (kg/m<sup>2</sup>)</b>	25 (23-28)	26(23-28)	0.500
Tumor infiltration		*	
cPR	9 (5)	45 (23)	0.000
I	36 (19)	44 (22)	
II	16 (9)	43 (21)	
III	118 (64)	69 (34)	
IV	6 (3)	0	

**Table 2 continued.** Patient characteristics

Variable	Internal validation (n=185)	External validation (n=201)	P-value
<b>Lymph node metastasis</b>			
N0	72 (39)	113 (54)	0.000
N1	51 (28)	52 (25)	
N2	41 (22)	22 (11)	
N3	21 (11)	3 (5)	
<b>Neoadjuvant therapy</b>			
None	114 (62)	20 (10)	0.000
Chemotherapy	63 (34)	20 (10)	
Chemoradiotherapy	8 (4)	167 (80)	
Radiotherapy	0	1 (<1)	

**Legend.** Table showing the baseline data. For continuous variables data shown represent median (interquartile range), all other data are presented as numbers (percentages).

**Abbreviations.** n, number; ASA score = American Society of Anaesthesiologist score; BMI: Body Mass Index; cPR = complet pathologic response\*missings, tobacco user n=1, alcohol user n=2, body mass index n=4, depth of tumor infiltration n=1.

**Table 3.** Surgical characteristics and clinical outcome

	Internal validation (n=185)	External validation (n=201)	P-value
<b>Surgical approach</b>			
Open Transhiatal	29 (16)	42 (20)	0.000
Open Transthoracal	11 (6)	1 (1)	
Minimally invasive, transhiatal	22 (12)	61 (29)	
Minimally invasive, transthoracic	123 (67)	104 (50)	
<b>Level of anastomosis</b>			
Intrathoracic	1 (1)	63 (30)	0.000
Cervical	184 (99)	144 (69)	
<b>Lymph nodes resected</b>	19 (13-27)	15 (9-23)	0.000
<b>Early start of oral intake</b>	0 (0)	29 (17)	0.000
<b>Clinical outcome</b>			
Anastomotic leakage	41 (22)	60 (29)	0.132
Recurrent laryngeal nerve injury	18 (10)	6 (3)	0.006
Cardiac arrythmia	23 (12)	34 (16)	0.215
Chyle leakage	26 (14)	25 (12)	0.537

**Table 3 continued.** Surgical characteristics and clinical outcome

	Internal validation (n=185)	External validation (n=201)	P-value
<b>Clinical outcome</b>			
Intensive care unit re-admission	34 (18)	46 (22)	0.275
Hospital admission time	17 (13-25)	13 (10-22)	0.000

**Legend.** Table showing the characteristics of the surgery performed and clinical outcome. For continuous variables data shown represent median (25th percentile-75th percentile), all other data are numbers (percentages). There were no missing data. Symbols.  $\phi$  = 2-sided chi-square test;  $Y$  = Mann-Whitney U Test.

**Table 4.** The revised Utrecht Pneumonia Score

	Treated (n =67)	Not treated (n=118)	OR (95% CI)	P-value
Temperature				
$\geq 36.1$ and $\leq 38.4$	45 (29)	112 (71)	reference	
$\leq 36.0$ and $\geq 38.5$	22 (79)	6 (21)	12.0 (2.8-51.1)	0.001
Leucocyte count				
$\geq 4.0$ and $\leq 11.0$	9 (11)	75 (89)	reference	
$< 4.0$ and $> 11.0$	58 (57)	43 (43)	6.0 (1.7-21.6)	0.006
Pulmonary radiography				
no infiltrate	13 (10)	113 (90)	reference	
diffuse or patchy infiltrate	31 (86)	5 (14)	37.4(11.0-127.4)	0.000
well circumscribed infiltrate	23 (100)	0 (0)	indefinite	0.000

**Legend.** Table showing independent odds ratio's of the components of the revised Utrecht Pneumonia Score, calculated by logistic regression. Values presented are numbers (percentages) and odds ratio's (95% confidence interval)

### Internal validation

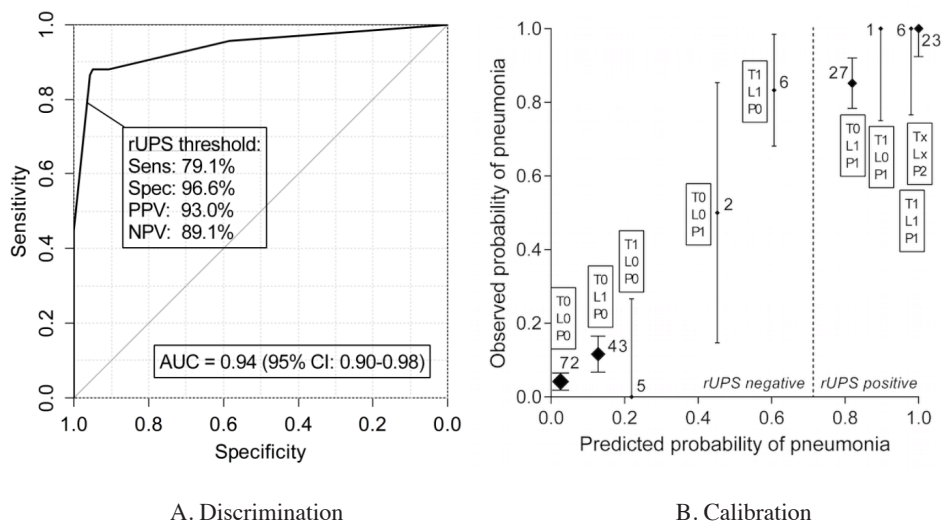
The UPS showed an excellent discriminatory ability and calibration in the development set (Figure 2A-B), with an apparent C-statistic of 0.94. Internal validation by bootstrapping resulted in an adjusted C-statistic of 0.94, representing hardly any optimism (i.e. 0.004) due to overfitting. Using the predefined cut-off value (at least 2 points of which at least 1 has to be assigned for pulmonary radiography) the sensitivity was 79% and the specificity was 97%. Slight miscalibration was observed in the group of patients (n=6) with 2 points assigned, based on leucocyte count and temperature and the group of patients (n=2) with 1 point only, assigned for radiography. The observed probability of pneumonia treatment was relatively



high in these two groups, whilst they were not classified as pneumonia by the UPS.

## External validation

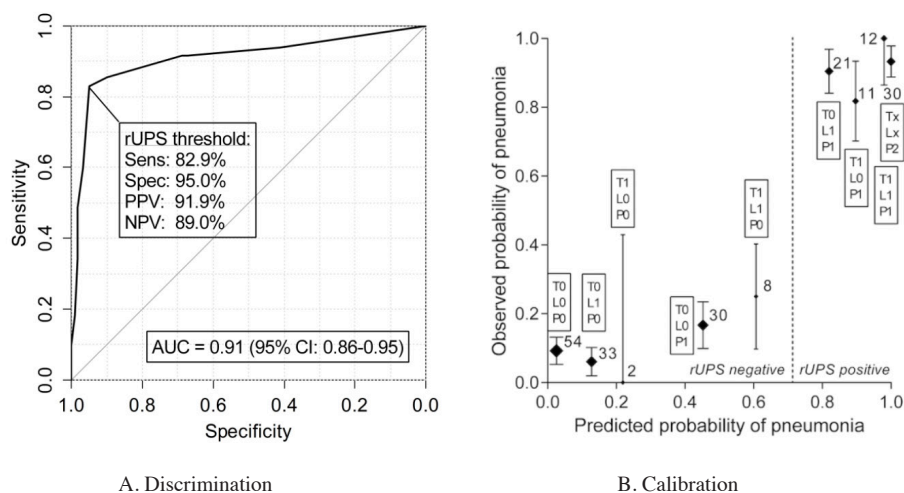
The revised UPS shows an excellent discriminatory ability (C-statistic of 0.91) and calibration in the validation set (Figure 3A-B). The sensitivity was 83% and the specificity was 95% for the predefined cut-off value. The calibration plot showed a low observed probability of pneumonia treatment in all patient groups that were classified as not having pneumonia, and a high probability of pneumonia treatment in all patient groups with a high predicted probability of pneumonia.



### Figure 2. Internal validation

**Legend.** The predicted probability of pneumonia is calculated by the sum of the predictive values of every independent variable multiplied by presence of every variable. The observed probability of pneumonia is the percentage of patients treated for pneumonia at the ward at any given point on the X-axis.

**Abbreviations.** Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; T, temperature; L, leukocytes; P, pulmonary radiography. AUC: aurea under the curve



**Figure 3.** External validation

**Legend.** The predicted probability of pneumonia is calculated by the sum of the predictive values of every independent variable multiplied by presence of every variable. The observed probability of pneumonia is the percentage of patients treated for pneumonia at the ward at any given point on the X-axis.

**Abbreviations.** Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value;

T, temperature; L, leukocytes; P, pulmonary radiography. AUC: area under the curve

## Discussion

The necessity for a uniform registration and definition of pneumonia following esophagectomy has become apparent by the article of Blencowe *et al.*<sup>10</sup> Now we show that the revised Uniform Pneumonia Score discriminates pneumonia from no pneumonia correctly in more than 90% of cases in internal and external validation sets with excellent calibration. This score consists of easy to measure variables; temperature, leucocyte count and pulmonary radiography findings.

The main finding of the study by Blencowe *et al* was that the large range in pneumonia definitions (16 different definitions) used by studies resulted in an equally large range of reported pneumonia rates (2%-39%).<sup>10</sup> Amongst others this study resulted in the initiative to standardize outcome reporting following esophagectomy, recently published as the international consensus on standardization of data collection for complications associated with esophagectomy.<sup>14</sup> However, for reasons not stated no consensus statement was made regarding pneumonia. For the definition of pneumonia the reader was referred to the guidelines of the American Thoracic Society and Infectious Diseases Society of America.<sup>15</sup> In these guidelines, focusing on ventilator associated pneumonia (VAP), the main reference is the clinical pulmonary infection score (CPIS), which has been extensively investigated for VAP.<sup>16-18</sup> The gold standard in these studies were postmortem investigation or microbiological results of bronchoalveolar lavage fluids, both not without flaws.<sup>16</sup> Also studies show that the CPIS criteria are not applicable to specific patient groups, such as trauma patients.<sup>19,20</sup> For hospital acquired pneumonia (HAP) no scoring system was proposed nor investigated. This shows the need for the present study in which hospital acquired pneumonia was investigated.

This study has several strengths. The model was developed and revised in a prospectively maintained database including a large cohort in relation to the number of variables studied. There was no loss to follow up and numbers of missing data were few. The variables used can be easily and objectively measured. In contrast to most studies the model was internally and externally validated, confirming the good discrimination and calibration in an external cohort of patients that underwent esophagectomy.

The main limitation of the present study was the lack of a gold standard for the diagnosis

of pneumonia. We chose to use the clinical decision to treat a suspected pneumonia as gold standard since in this decision making process all factors are accounted for by the attending clinician.

For research purpose however a clearer definition is needed. Therefore, we aimed to determine what parameters accurately determined the outcome of this decision making process. Van der Sluis *et al.* recently showed that the outcome of sputum culture is not relevant, probably because the sensitivity is insufficient and the results become available after the decision to treat pneumonia has been made.<sup>8</sup> Broncho-alveolar lavage is considered to be too invasive to use as routine diagnostic.

Another interesting method to create a gold standard would be to create a consensus statement of several experts via a Delphi procedure.<sup>21</sup> It would be interesting to use this for further validation of the Utrecht Pneumonia Score. Finally, the observed miscalibration was very low, especially in the external validation study, indicating an excellent model for determining pneumonia. The observed miscalibration mainly existed in patients in the development data set that scored one point for leucocytes and one point for temperature but 0 points for pulmonary radiography. Most probably pneumonia treatment was initiated in these patients before infiltrates were visible at pulmonary radiography. Perhaps this was based on a not measured other factor, such as coughing, which was not included in the (revised) Utrecht Pneumonia Score since it was considered to be subjective. Furthermore the calculated odds ratio of 37.4 for pulmonary radiography should be considered a rather unstable estimation due to the low numbers of false-positive and false-negative pulmonary radiography test results in this cohort, as reflected by the wide 95% CI ranging from 11.0 to 127.4. However, even the lower bound of the 95% CI suggests that the true underlying OR in the population is likely very high. This supports the requirement of a pulmonary radiography score of  $\geq 1$  in the scoring system for pneumonia.

The incidence of pneumonia in this study as scored by the UPS is at the high end of the range of pneumonia rates published in literature (2-39%)<sup>10</sup>. As shown by Blencowe *et al* the most obvious underlying reason is the different definitions used in other studies.<sup>10</sup> Another study

by van der Sluis *et al* showed that adding the requirement of a positive sputum culture decreased the pneumonia incidence from 36 to 19%.<sup>8</sup> A relevant outcome of a study in which therapies for pneumonia are investigated may consist of a reduced incidence but also of a reduced severity of postoperative pneumonia. Reporting of pneumonia using the UPS does not include information on the severity of pneumonia. This can be solved by grading the severity of UPS defined pneumonia using the validated revised Clavien-Dindo classification of surgical complications or Accordion classification of complications.<sup>22-24</sup>

## Conclusion

The UPS is the first internally and externally validated method that accurately predicts treatment for pneumonia following esophagectomy. Because this score proves to represent the decision-making process of clinicians to treat for pneumonia on an inter-hospital level, the UPS can serve as a means to define post-esophagectomy pneumonia in research. Future studies and audits reporting postoperative outcomes of esophagectomy are encouraged to provide pneumonia incidences as defined by this score to improve inter-study and inter-hospital comparability.

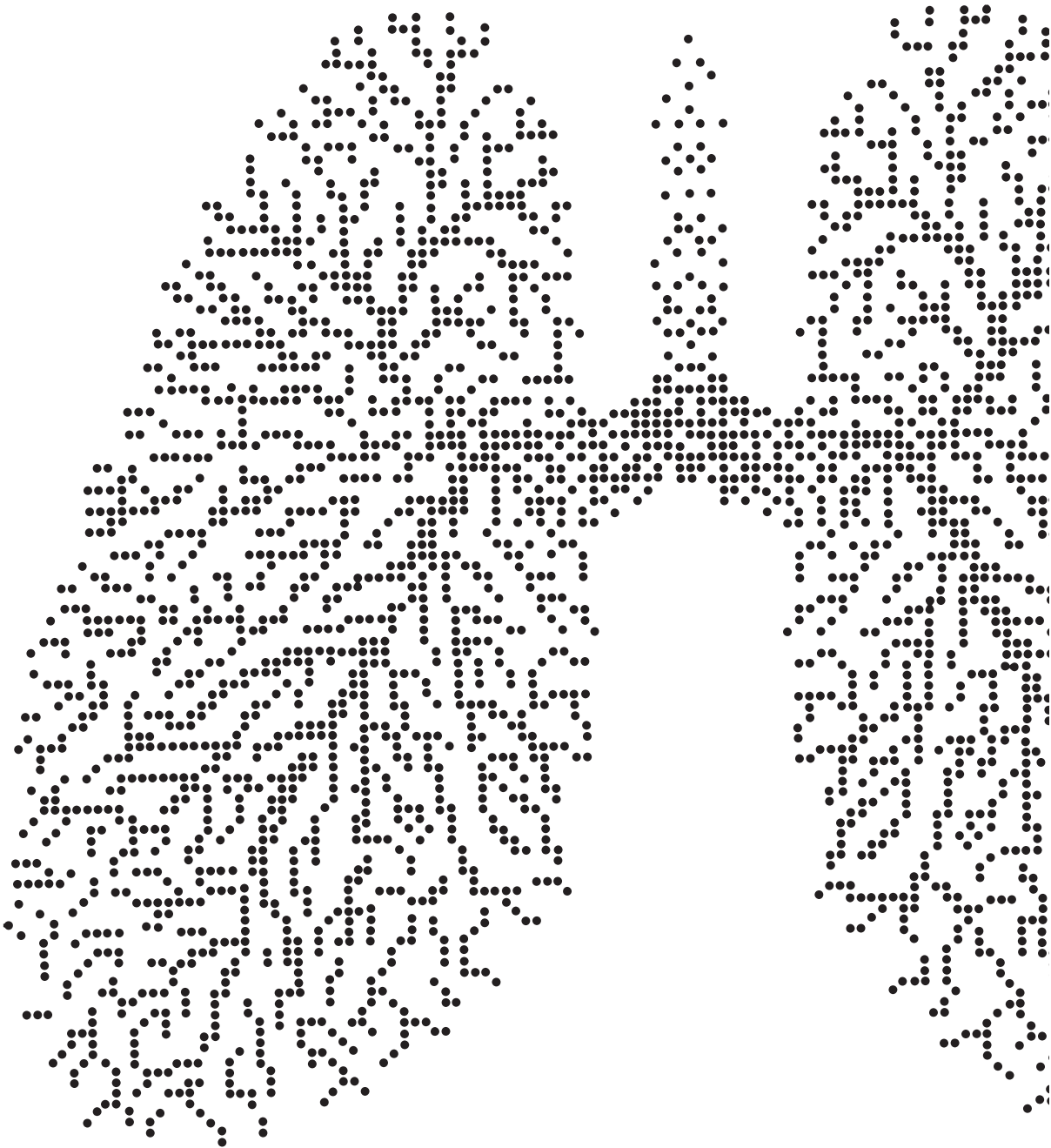
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# Chapter 10

Defining pneumonia  
after esophagectomy  
for cancer:  
Validation of the Uniform  
Pneumonia Score in a high  
volume center in North  
America

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## Abstract

**Background** Surgery is a central component of multimodality therapy for esophageal and gastroesophageal junction cancer. Pneumonia is a common sequela of esophagectomy, leading to increased time in intensive care unit, hospital stay, readmission rates and postoperative mortality. Developing strategies to reduce pneumonia after esophagectomy is hampered by the absence of a standardized methodology for defining pneumonia. This study aimed to validate the Uniform Pneumonia Score (UPS) in a high volume center in the USA (United States of America).

**Materials & Methods** The UPS was developed to define pneumonia after esophagectomy for cancer, and is based on assessment of temperature (°C), leukocyte count ( $\times 10^9/L$ ), and pulmonary radiography. The UPS has been validated utilizing a prospective database of esophageal cancer patients treated in a high volume esophagectomy center in the USA between 2010 and 2015.

**Results** One hundred ninety-three consecutive patients were included and 21 (10.9%) were treated for pneumonia. The UPS was able to predict treatment for suspected pneumonia with a sensitivity of 85.7%, specificity of 97.1%, positive predictive value of 78.3%, and a negative predictive value of 98.2%. The diagnostic accuracy was 95.9%.

**Conclusions** The UPS demonstrated to be a reliable scoring system to define pneumonia after esophagectomy for cancer. Global application of this model will standardize the definition of pneumonia after esophagectomy and will improve outcome reporting and comparisons of complications between individual institutions, clinical trials and national audits.

# Background

Esophagectomy remains an important component of multimodality treatment for regional esophageal or gastroesophageal junction (GEJ) cancer.<sup>1</sup> However, the associated morbidity and mortality can be significant.<sup>2-5</sup> Pulmonary complications, primarily pneumonia, are frequently observed and may increase mortality and prolong intensive care unit- and hospital stay.<sup>6-8</sup> This highlights the need to develop new strategies to reduce pulmonary complications after esophagectomy. Unfortunately, research and quality improvements in pulmonary complications after esophagectomy are hampered by the lack of a standardized methodology for defining postoperative pneumonia. In current literature 16 different, non-validated, definitions are used for pneumonia, leading to a wide variation of reported pneumonia incidences (2% to 39%).<sup>8,9</sup> The variation in definitions have made it impossible to assess and compare pneumonia-related outcomes across individual institutions, clinical trials, and national audits.

The lack of a validated and internationally accepted and used definition for pneumonia after esophagectomy led to the initiative by van der Sluijs et al.<sup>6</sup> to create an objective and easy applicable scoring system to define pneumonia. This scoring system, the Utrecht Pneumonia Score, was revised and both internally (University Medical Center Utrecht) and externally (Catharina Hospital Eindhoven), resulting in the Uniform Pneumonia Score (UPS) (Table 1).<sup>10</sup> The current study aims to validate the UPS in a geographically distinct cohort of esophagectomy patients from a high volume center in the United States of America.

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Table 1. Uniform Pneumonia Score		
Diagnostic determinant	Uniform Pneumonia Score	
	Range	Score
Temperature [°C]	≥ 36.1 and ≤ 38.4	0
	≤ 36.0 and ≥ 38.5	1
Leukocyte count [x10 <sup>9</sup> /L]	≥ 4.0 and ≤ 11.0	0
	< 4.0 or > 11.0	1
Pulmonary radiography	No infiltrate	0
	Diffuse (or patchy) infiltrate	1
	Well-circumscribed infiltrate	2

**Legend.** A sum score of 2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography indicates treatment of pneumonia.

## Materials & Methods

### Patients and data

Data of all consecutive patients who underwent an esophagectomy for resectable esophageal or GEJ cancer (Siewert I and Siewert II) in a tertiary referral center (Virginia Mason Medical Center, Seattle, WA) between January 2010 and January 2016 were prospectively entered into an IRB approved database. Database entries included standard patient characteristics, and intraoperative and postoperative data. UPS specific variables (temperature [°C], leukocyte count [ $\times 10^9/L$ ] and pulmonary radiography findings) were retrospectively collected from the computerized medical records, similarly to the previous validation study.<sup>10</sup> For pulmonary radiography findings both chest X-rays and CT scans were taken into account when available. In patients treated with antibiotics following the diagnosis of pneumonia, temperature, leukocyte count, and pulmonary radiography findings were collected on the day of treatment initiation. In patients not treated for pneumonia, temperature, leukocyte count, and pulmonary radiography findings were collected from the medical records on the fourth postoperative day to ensure sufficient time from ICU discharge.

Thus, similar to the design study and previous validation study, no possible operation- or ventilator-associated abnormalities were present on pulmonary radiography. If variables were not available on day 4 postoperatively, data was collected on the closest consecutive day, on which the variable of interest was available. After exclusion of patients with missing values for model variables, complete case analysis was performed.

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The current study was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and received ethical approval from the local medical ethical committee (Institutional Review Board number 17-072). The need for informed consent was waived. Patients underwent either an open transhiatal, Ivor Lewis-, or left thoracoabdominal esophagectomy with a two-field lymphadenectomy. Neoadjuvant chemotherapy regimens at Virginia Mason Hospital & Medical Center routinely consists of 5 cycles of either the combination of Carboplatin and Taxol or Cisplatin and 5FU delivered with radiotherapy with a typical dose of 50.4 gray delivered in 28 fractions. All patients were managed according to the latest version of the Virginia Mason Medical Center esophagectomy (enhanced recovery) clinical pathway.<sup>11</sup>

## Outcomes

The primary outcomes were sensitivity, specificity, accuracy, positive predictive- and negative predictive value of the UPS. Furthermore, calibration and discriminatory ability were assessed. In line with previous studies (and in the absence of a well-defined gold standard for the diagnosis of pneumonia after esophagectomy), the outcome measure ‘pneumonia’ was defined as the clinical decision to initiate antibiotic treatment for suspected pneumonia.<sup>6, 10</sup> Secondary outcomes included pulmonary complications other than pneumonia, anastomotic leakage, chylothorax, recurrent laryngeal nerve injury, cardiac complications, length of hospital stay, and length of ICU stay.<sup>9</sup>

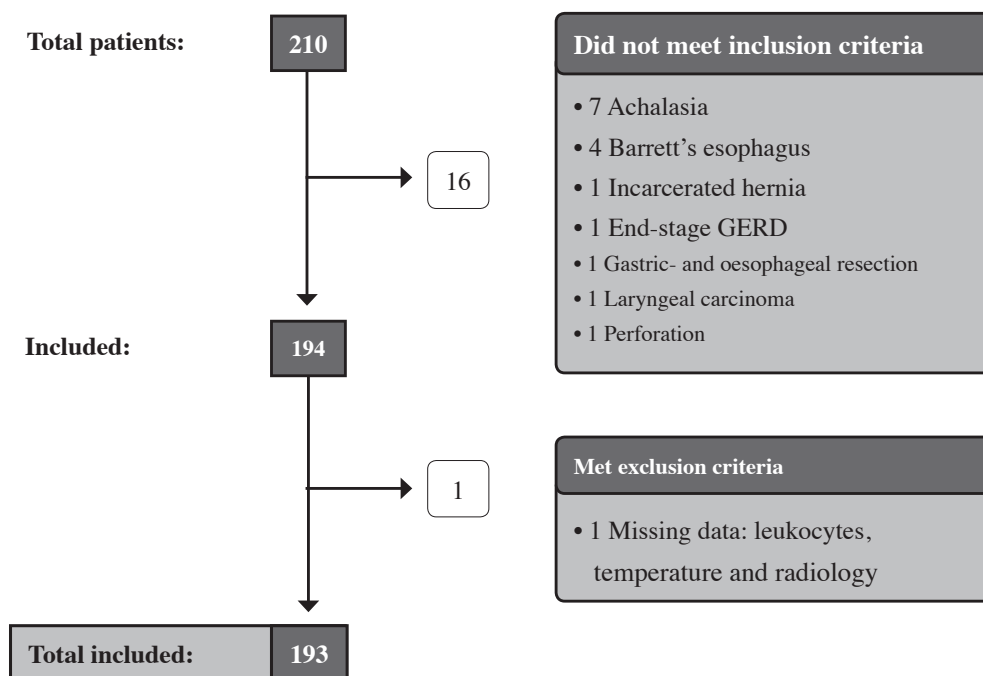
## Statistical Analysis

Data were analyzed using SPSS for Windows, version 22.0 (IBM corp., Armonk, New York) and R 3.1.2 open-source software (<http://www.R-project.org>). Analysis and reporting were performed in accordance with the TRIPOD statement.<sup>12</sup> Patient and treatment-related characteristics as well as postoperative outcomes besides pneumonia were compared between patients who were treated for pneumonia and patients who were not, in order to provide insight in potential differences. Categorical data was compared using the chi-square test or Fisher’s exact test, as appropriate. Continuous data were compared using the Mann-Whitney-U test or Student’s T-test for non-parametric or parametric variables, respectively. The model performance of the UPS was assessed for discriminatory ability and calibration. Discrimination is the ability to distinguish a patient with the outcome from a patient without the outcome, which was assessed using the concordance (C) statistic extracted from receiver operating characteristic (ROC) curve analysis.<sup>13</sup> The agreement between the predicted probability of pneumonia by the model and the observed probability is indicated by calibration, and was determined by visual inspection of calibration plots.

## Results

### Patient and treatment characteristics

Figure 1 shows the process of patient selection. A total of 210 consecutive patients underwent esophagectomy at Virginia Mason Medical Center between January 2010 and January 2016. Sixteen patients were excluded because they underwent esophagectomy for benign disease and 1 patient was excluded due to missing UPS specific data. Hence, 193 patients were included for analyses (Figure 1). Mean age of the included patients was 66.1 ( $\pm 5.1$ ) years, 60.6% of patients were classified as ASA III, 36.3% of the patients had a pT3 tumor, and 69.9% underwent neoadjuvant chemoradiation (Table 2). Across the 193 patients in this study, 21 (10.9%) underwent treatment for pneumonia. Patients with a pre-existing comorbidity of COPD or a history of smoking had a significantly higher incidence of pneumonia (Table 2).



**Figure 1:** Flowchart

*Legend. Abbreviations. GERD: gastroesophageal reflux disease*



All but one patient received a gastric reconstruction after esophagectomy. Approximately half of the patients (48.2%) underwent an open Ivor-Lewis procedure (intrathoracic anastomosis) and the other half (48.2%) underwent an open left thoracoabdominal operation with a cervical anastomosis. The remaining 3.6% underwent an open transhiatal esophagectomy. An R0 resection was achieved in 97.4% of patients and the median (range) lymph node yield was 21 (5-49) (Table 3).

**Table 2.** Patient characteristics

	Total	Antibiotics for pneumonia		<i>P</i>
	(n=193) (%)	Yes (n=21) (%)	No (n= 172)(%)	
Female	41 (21.4)	4 (19.0)	37 (21.5)	0.794
Male	152 (78.6)	17 (81.0)	135 (78.5)	
<b>Age</b>	66.1 ±9.6	65 ±11.2	66 ±9.4	0.256
<b>BMI</b>	27.7 ±5.1	27.1 ±6.4	27.8 ±5.0	0.338
<b>ECOG score</b>				
O	94 (48.7)	9 (42.9)	85 (49.4)	0.559
I	84 (43.5)	10 (47.6)	74 (43.0)	
II	14 (7.3)	2 (9.5)	12 (6.9)	
III	1 (0.5)	0 (0)	1 (0.6)	
<b>ASA score</b>				
II	76 (39.4)	7 (33.3)	69 (40.1)	0.549
III	117 (60.6)	14 (66.7)	103 (59.9)	
<b>Alcohol user</b>	174 (90.2)	19 (90.5)	155 (90.1)	0.980
<b>Nicotine user</b>				
Current	30 (15.5)	9 (42.9)	21 (12.2)	<0.001
Previous	121 (62.7)	12 (57.1)	109 (63.4)	
Never	42 (21.8)	0 (0.0)	42 (24.4)	
<b>Comorbidity</b>				
Cardial	44 (22.8)	5 (23.8)	39 (22.7)	0.907
Vascular	109 (56.5)	11 (52.4)	98 (57.6)	0.688
Diabetes	43 (22.8)	6 (28.6)	37 (21.5)	0.318
Asthma	17 (8.8)	1 (4.8)	16 (9.3)	0.488
COPD	20 (10.3)	5 (23.8)	15 (8.8)	0.032

**Table 2 continued.** Patient characteristics

	Total	Antibiotics for pneumonia		P
	(n=193) (%)	Yes (n=21) (%)	No (n= 172)(%)	
Pathological T-stage				
cPR	42 (21.8)	5 (23.8)	37 (21.5)	0.312
Tis	1 (0.5)	0 (0)	1 (0.6)	
T1	43 (22.3)	6 (28.6)	37 (21.5)	
T2	35 (18.1)	5 (23.8)	30 (17.4)	
T3	70 (36.3)	5 (23.8)	65 (37.8)	
T4	1 (0.5)	0 (0)	1 (0.6)	
Tx	1 (0.5)	0 (0)	1 (0.6)	
Pathological N-stage				
N0	106 (54.9)	14 (66.7)	92 (53.5)	0.172
N1	44 (22.8)	5 (23.8)	39 (22.7)	
N2	29 (15.0)	2 (9.5)	27 (15.7)	
N3	12 (6.2)	0(0)	12 (7.0)	
Nx	2 (1.1)	0(0)	2 (1.1)	
Histology				
Adenocarcinoma	168 (85.7)	19 (90.5)	146 (84.9)	0.746
Squamous cell carcinoma	26 (13.3)	2 (9.5)	24 (14.0)	
Other	2 (1.0)	0 (0.0)	2 (1.2)	
Neoadjuvant therapy				
None	53 (27.5)	7 (33.3)	46 (26.7)	0.624
CTx	5 (2.6)	1 (4.7)	4 (2.3)	
CRTx	135 (69.9)	13 (62.0)	122 (71.0)	

**Legend.** Table showing the baseline data. Data are presented as mean ( $\pm$  standard deviation) or as numbers (percentages).

**Abbreviations.** M, male; F, female; ; n, number; ASA score = American Society of Anaesthesiologist score; BMI = Body Mass Index (kg/m<sup>2</sup>); ECOG = Eastern Cooperative Oncology Group; CTx = Chemotherapy; CRTx = Chemoradiation.

Significantly more patients who were clinically diagnosed with pneumonia and consequently underwent antibiotic treatment were diagnosed with a pneumothorax (23.8% versus 9.3% (P=0.044)), pleural effusion requiring treatment (28.6% versus 10.6% (P=0.018)), reintubation (28.6% versus 1.7% (P<0.001)), and recurrent laryngeal nerve injury (4.8% versus 0.0% (P=0.004)) when compared to the patients who were not treated for pneumonia. A patient

who developed pneumonia demonstrated a significant longer hospital stay (12 (7-112) days versus 7 (5-43) days ( $P<0.001$ )). (Table 4) One (0.5%) patient died within 30 days after surgery and three (1.6%) patients died within 90 days after surgery.

**Table 3.** Surgical characteristics

	Total (n =193) (%)	Antibiotics for pneumonia		<i>P</i>
		Yes (n = 21 ) (%)	No (n = 172) (%)	
<b>Surgical approach</b>				
Ivor Lewis	93 (48.2)	9 (42.9)	84 (48.8)	0.410
Left thoracoabdominal	92 (48.2)	10 (47.6)	82 (47.6)	
Transhiatal	8 (3.6)	2 (9.5)	6 (3.5)	
<b>Gastric conduit reconstruction</b>	192 (99.5)	1 (4.8)	0 (0.0)	0.004
<b>Jejunostomy</b>	140 (72.5)	17 (81.0)	123 (71.5)	0.360
<b>OR time (min)</b>	401 (244 - 664)	446 (344-615)	401 (244-664)	0.110
<b>Estimated blood loss (cc)</b>	150 (50 - 700)	200 (75-500)	150 (50-700)	0.081
<b>Radicality</b>				
R0	188 (97.4)	21 (100.0)	167 (97.1)	0.429
R1	5 (2.6)	0 (0.0)	5 (2.9)	
<b>Lymph node yield</b>	21 (5-49)	22 (10-44)	21 (5-49)	0.446

**Legend.** Table showing the baseline data. For continuous variables data shown represent median (interquartile range), all other data are presented as numbers (percentages).

**Abbreviations.** OR = Operation Room, cc= milliliter.

## External Validation

Pneumonia defined by the UPS demonstrated a sensitivity of 85.7% and a positive predictive value of 78.3%. The specificity was 97.1% and the negative predictive value 98.2% (Table 5). The diagnostic accuracy was 95.9%. Furthermore, both the discriminatory ability (C-statistic of 0.97) (Figure 2a) and calibration (Figure 2b) were very satisfactory. In patients not classified as being treated for pneumonia, a low observed probability of pneumonia was demonstrated in the calibration plot. The calibration plot also showed a high probability of pneumonia treatment in all patients with a positive UPS. Of the UPS negative patients, none of the T0L0P0-, T0L1P0- and T1L0P0 patients and, 4 (11.2%) out of 35 T0L0P1 patients underwent antibiotic treatment. In the UPS positive group, the majority of the T0L1P1 and

TXLXP2 patients received antibiotic treatment. Only 1 patient was scored T1L0P1 and did not receive antibiotic treatment (table 2b).

**Table 4.** Clinical outcomes

	Total (n = 193) (%)	Antibiotic treatment for pneumonia		<i>P</i>
		Yes (n = 21) (%)	No (n = 172) (%)	
<b>Postoperative complications total</b>	108 (56.0)	n.a.	n.a.	n.a.
<b>Pneumothorax</b>	21 (10.9)	5 (23.8)	16 (9.3)	0.044
<b>Pleural effusion requiring treatment</b>	24 (12.4)	6 (28.6)	18 (10.5)	0.018
<b>Reintubation</b>	9 (4.7)	6 (28.6)	3 (1.7)	<0.001
<b>Anastomotic leakage</b>	16 (8.3)	3 (14.3)	13 (7.6)	0.291
<b>Chyle leakage</b>	9 (4.7)	1 (4.8)	8 (4.7)	0.982
<b>Recurrent laryngeal nerve injury</b>	1 (0.5)	1 (4.8)	0 (0)	0.004
<b>Atrial fibrillation</b>	44 (22.8)	7 (33.3)	37 (21.5)	0.223
<b>Hospital stay</b>	7 (5-115)	12 (7-115)	7 (5-43)	<0.001
<b>ICU stay</b>	1 (0-22)	1 (1-15)	1 (0-22)	0.234

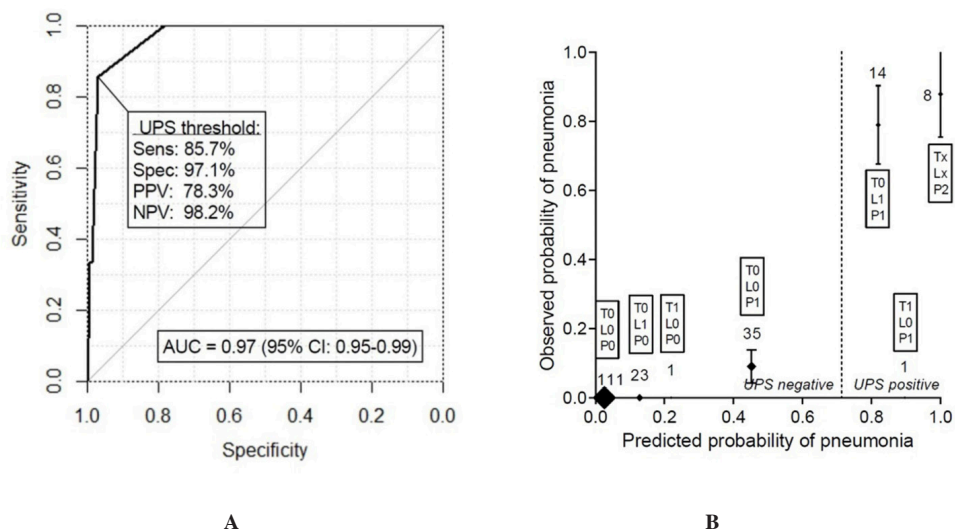
**Legend.** For continuous variables data shown represent median (range), all other data are presented as numbers (percentages).

**Abbreviations.** ICU = Intensive Care Unit; n.a. = not applicable

**Table 5.** Diagnostic performance

	Antibiotics for pneumonia	
	Yes (n = 21 )	No (n = 172)
Uniform pneumonia score		
<b>Positive</b>	18 (85.7%)	5 (2.9%)
<b>Negative</b>	3 (14.3%)	167 (97.1%)

**Legend.** Sensitivity (85.7%), predictive value (78.3%), specificity (97.1%), negative predictive value (98.2%), accuracy (95.9%)



**Figure 2:** Discrimination (A) and Calibration (B)

**Abbreviations:** UPS : Uniform Pneumonia Score. Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

## Discussion

In accordance with a previously published external validation analysis, this study demonstrated the UPS to be an accurate dichotomous scoring system to define pneumonia after esophagectomy for esophageal and GEJ cancer.<sup>6, 10</sup> In the previous validation study the UPS demonstrated a sensitivity of 79.1% and a specificity of 96.6% in the University Medical Center Utrecht and a sensitivity of 82.9% and specificity of 95.0% in the Catharina Hospital Eindhoven, both high volume esophagectomy centers in the Netherlands.<sup>10</sup> To support general applicability of any scoring system, external validation, achieved by evaluating the model performance in differing clinical settings, is essential.<sup>14</sup> The current study showed that the UPS can be a valuable tool for investigating pneumonia in a distinct patient population, using a different surgical approach and postoperative clinical pathway. Moreover, the UPS was found to be an easy applicable scoring system, since the measured variables (temperature, leucocyte count and pulmonary radiography findings) were routinely available as reflected by the fact that only one patient was excluded due to missing variables.

The results of this study support the implementation and application of the UPS in research on outcomes after esophagectomy for cancer. The need for a uniform definition of post-esophagectomy pneumonia has been demonstrated by a meta-analysis, which showed that between 2004 and 2009, of 56 studies reporting on pneumonia after esophagectomy only 18 defined pneumonia using 16 different definitions. This has resulted in a wide range of pneumonia incidence (2-39%) in previous reports of esophagectomy outcomes. The authors demonstrated, that the reporting of morbidity and mortality after esophagectomy for esophageal cancer lacks standard definitions, making it difficult to compare results, and concluded that uniform definitions for complications following esophagectomy should be developed.<sup>8</sup> This led to the development of a specific scoring model to define pneumonia after esophagectomy in 2014 (Utrecht Pneumonia Score) and the initiative of the ECCG to standardize reporting of complications following esophagectomy.<sup>6, 9</sup> The results of the Delphi survey, published as the “International Consensus on Standardization of Data Collection for Complications Associated with Esophagectomy”, is considered to be the standard guideline for reporting complications after esophagectomy and is now also used in nationwide registries.<sup>9, 15</sup> Following the agreement to develop a comprehensive complication list, and in an effort to avoid confusion regarding already existing definitions, the participating centers decided to

link many complications, including pneumonia, to standard definitions. Pneumonia was defined by an internationally accepted definition, published by the American Thoracic Society and the Center for Disease Control and Prevention.<sup>9, 16</sup> However, these guidelines focused on Ventilator-associated Pneumonia (VAP), defining pneumonia according to the clinical pulmonary infection score (CPIS). The CPIS has been developed in patients with VAP, without validation in patients with pneumonia.<sup>17-19</sup> Moreover, it has been demonstrated that the CPIS is not generally applicable, since its validation in trauma patients failed.<sup>20</sup> Hence, a general and widely accepted definition for pneumonia after esophagectomy was still lacking. To fill the gap, the Utrecht Pneumonia Score was revised, and an internal and external validation of the revised score led to the introduction of the Uniform Pneumonia Score in 2016.<sup>10</sup>

The UPS consists out of three variables; leukocytes, temperature and pulmonary radiography. Sputum culture is not included in the UPS since, as previously demonstrated, a positive sputum culture was not significant associated with the clinical diagnosis of pneumonia in multivariate analysis. Furthermore, in approximately a quarter of patients treated for pneumonia sputum culture results are not available, making it an insufficient variable for defining pneumonia in retrospective research.<sup>6</sup>

Since pneumonia is the most frequently observed complication after esophagectomy for cancer, it often serves as the primary outcome of comparative surgical studies.<sup>8</sup> The UPS has already been utilized as a primary outcome measure in multiple retrospective and prospective studies.<sup>21-26</sup> However, several landmark trials in which pneumonia was the primary outcome measure and on which current practice is based, like the TIME trial<sup>27</sup> and the MIRO trial<sup>2, 28</sup>, have utilized different and non-validated definitions.

The UPS has proven to be an accurate definition for pneumonia after esophagectomy in different centers within the Netherlands. It is a dichotomous scoring system, which can be applied easily in clinical practice. However, it only facilitates quantifying the diagnosis of pneumonia. Since it does not stratify on the basis of severity, grading of pneumonia severity may be scored using the Clavien-Dindo classification of surgical complications.<sup>29, 30</sup>

In the current study, the UPS was validated in a geographically distinct external cohort in the

USA.<sup>10</sup> Esophagectomies at this North American center were performed open and peri- and postoperative care was guided, in contrast to the previous validation study, by an enhanced recovery after surgery (ERAS) protocol.<sup>11</sup> The ERAS protocol aims to optimize perioperative care by minimizing surgical stress and complications and accelerate recovery.<sup>31</sup> In the previous validation study no ERAS protocol were used. This may be an important reasons why the incidence of pneumonia in the present study was remarkably lower (11.9%) when compared to pneumonia rates in the previous validation study (36% in the University Medical Center Utrecht and 40% in the Catharina Hospital Eindhoven).<sup>10</sup> Also, in the present cohort, the UPS was able to provide a reasonably accurate definition for pneumonia after esophagectomy, which shows its potential for broader application. Standardized definitions for postoperative complications will increase accuracy of future research and quality initiatives.

The strength of the current study is the evaluation of a prospective dataset without loss to follow-up, containing detailed information on postoperative complications from a high-volume esophageal cancer care center. Furthermore, the ease of score-variable collection is demonstrated, facilitating the wide implementation of the UPS in both retrospective and prospective studies. Since UPS specific variables are collected routinely on the fourth postoperative day in most hospitals, also nationwide registries can make use of the UPS. Despite this, certain limitations apply to the current analysis. The gold standard for diagnosing pneumonia in the current study was the clinical decision to initiate treatment for suspected pneumonia. This subjective definition has been used in previous studies, and constitutes the only definition, in which, all factors are accounted for by the attending physician. Since there is no current gold standard for the definition of post-esophagectomy pneumonia, this definition remains the best standard to validate the UPS, which is designed to fill this gap. Furthermore, the incidence of pneumonia was 10.9% in the present study, hence relatively few events were observed. However, for external validation studies, formal sample size calculations for the number of events based on statistical power considerations are not well investigated.<sup>14</sup>

Within the context of these limitations, the present study showed the UPS to be an accurate, objective, and easy to implement scoring system to define pneumonia after esophagectomy in esophageal cancer research. Therefore we encourage the application of the UPS in future



esophageal cancer research and nationwide registries reporting on outcomes after esophagectomy.

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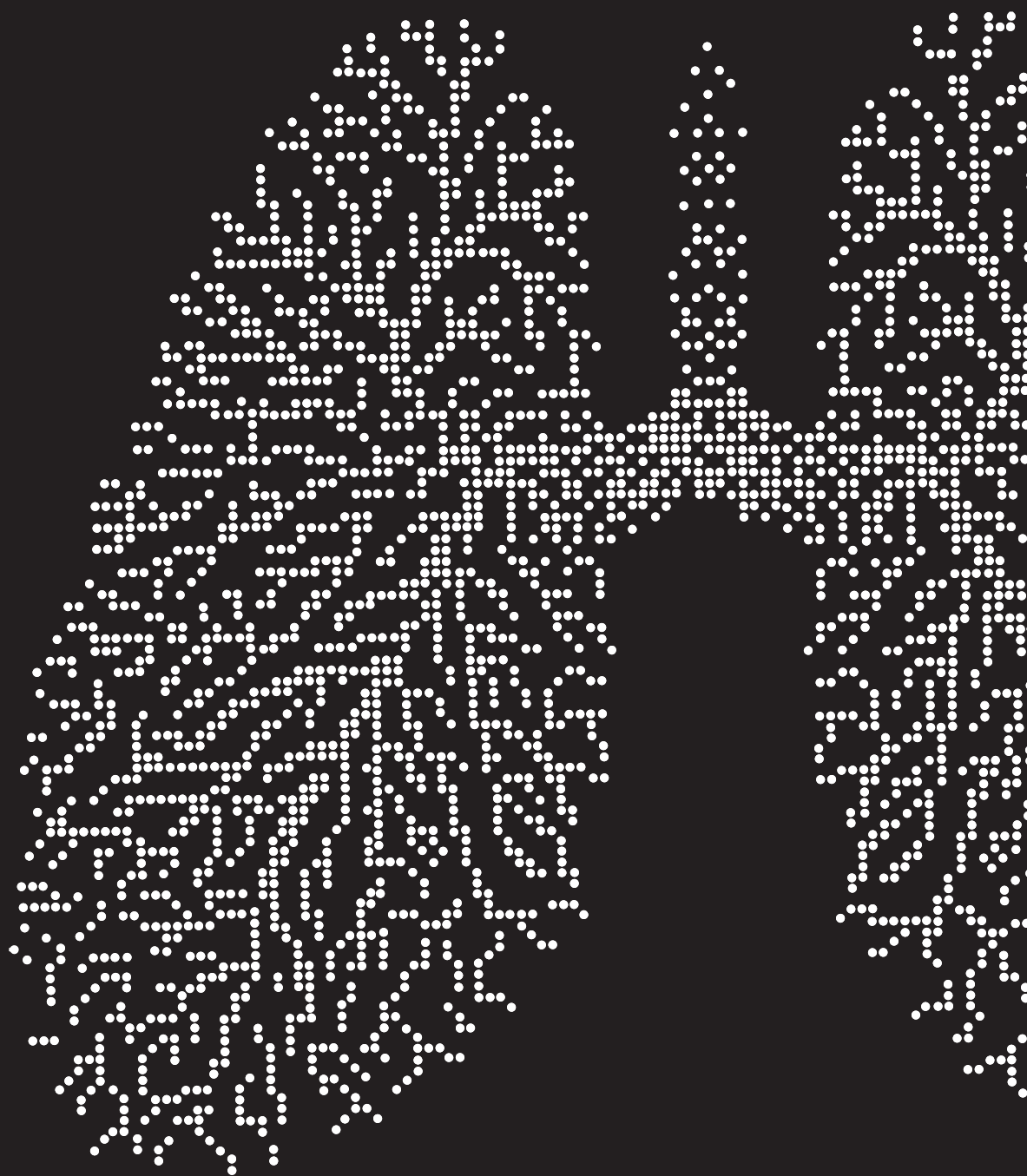
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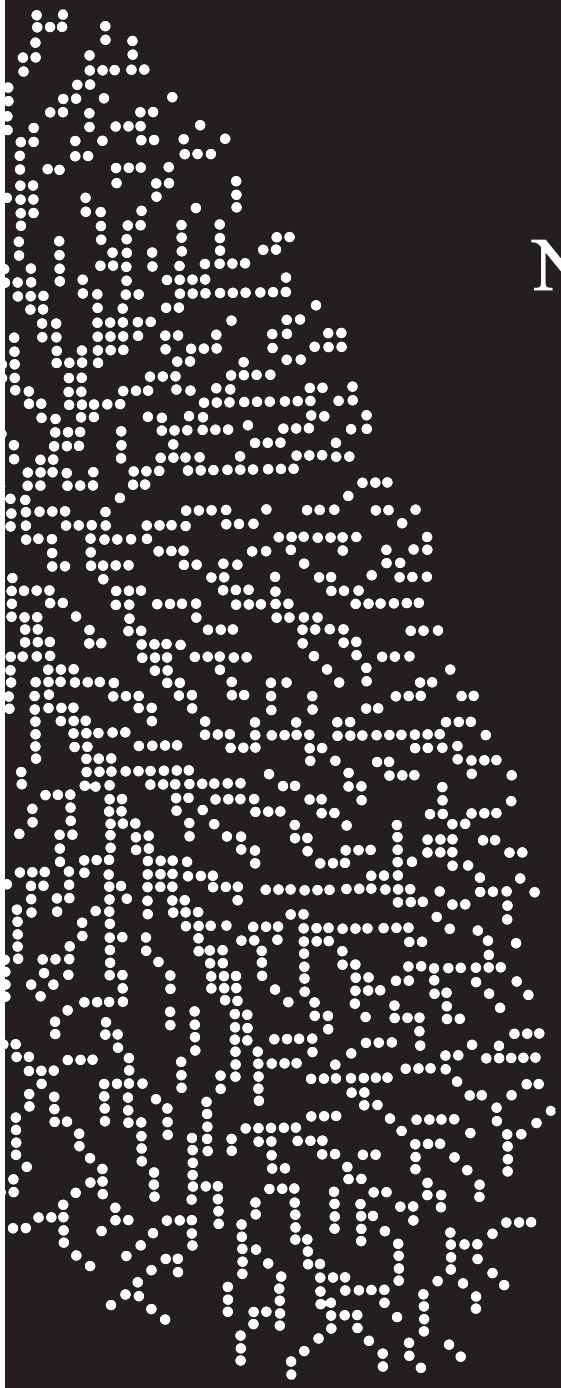
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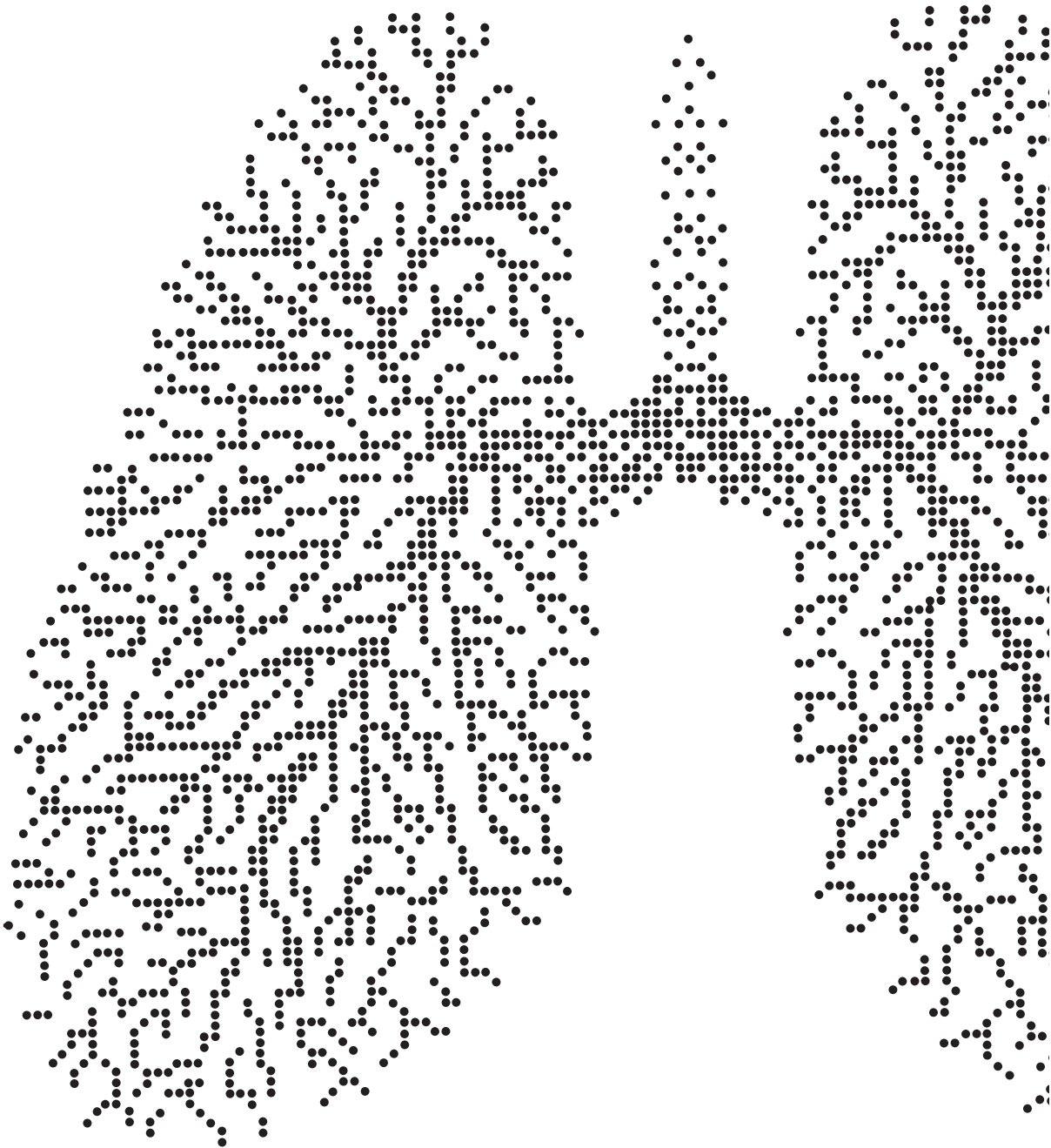




# PART III

## NEUROIMMUNITY









# Chapter 11

Aggravation of LPS-induced  
acute lung injury depends on  
the location of vagotomy and  
is partly mediated  
by  $\alpha 7$  nicotinic  
acetylcholine receptors

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## Abstract

**Background:** Although pulmonary complications frequently occur following esophagectomy, the etiology is indefinite. We hypothesize that the vagotomy performed as part of the procedure may play a role since the autonomic nervous system regulates release of pro-inflammatory cytokines via  $\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7$ nAChR) on macrophages. The aim of the current study was to evaluate the effect of the level of vagotomy on lipopolysaccharide (LPS)-induced acute lung injury.

**Materials & Methods:** Rats (N=72) were randomized into the following groups: sham procedure, bilateral cervical vagotomy (CVGX), abdominal subdiaphragmatic vagotomy group (AVGX), CVGX +  $\alpha 7$ nAChR-agonist, sham +  $\alpha 7$ nAChR-antagonist, and CVGX +  $\alpha 7$ nAChR-antagonist. Rats were administered LPS intratracheally following vagotomy. A pulmonary function test was conducted 270 minutes after administration of LPS, and 30 minutes afterwards rats were euthanized to assess parameters of organ injury and dysfunction.

**Results:** CVGX resulted in a significant increase in pulmonary resistance, lung injury score and macrophages in bronchoalveolar lavage fluid (BALF) in comparison to the AVGX- and sham procedure. The total number of lymphocytes in the BALF and total number of mononuclear cells in blood in the CVGX group were significantly increased compared to the sham group. In contrast, cervical vagotomy had no significant influence on TNF- $\alpha$  and IL-6 levels in BALF and blood. Both the  $\alpha 7$ nAChR-agonist and antagonist did not significantly affect LPS-induced acute lung injury.

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**Conclusion:** Vagotomy above the level of the pulmonary branches of the vagus nerve decreases pulmonary function and increases LPS-induced acute lung injury. Vagotomy may therefore be an important factor in the occurrence of pulmonary complications following esophagectomy.

## Background

Esophagectomy is the cornerstone of multimodality curative treatment for resectable esophageal cancer.<sup>1,2</sup> This complex procedure is frequently associated with pulmonary complications, which increase intensive care unit readmission rate, length of hospital stay, and mortality.<sup>3,4</sup> Although many factors have been associated with the occurrence of postoperative pulmonary complications, the exact pathogenesis is unknown.<sup>5</sup> However, pulmonary complications after esophagectomy appear to be associated with an unbalanced inflammatory response.<sup>6</sup> An increased inflammatory response within 48 hours after esophagectomy has been demonstrated to independently predict the occurrence of pulmonary complications.<sup>7,8</sup>

This inflammatory response is regulated by many factors, such as the autonomic nervous system. During the past decades, stimulation of efferent vagus nerve fibres has been shown to effectively inhibit the inflammatory response by release of acetylcholine that binds to the  $\alpha 7$  nicotinic acetylcholine receptor ( $\alpha 7$ nAChR) expressed on inflammatory cells.<sup>9-11</sup> Not only neurogenic, but also pharmacological and nutritional stimulation of this so-called cholinergic anti-inflammatory pathway reduces release of pro-inflammatory mediators in research models of sepsis, hemorrhagic shock and ventilator-induced lung injury.<sup>12-15, 16</sup>

Pulmonary branches of the vagus nerve are often transected as part of an esophagectomy and its concurrent lymphadenectomy.<sup>17</sup> Recent literature indicates that a significant part of the pulmonary branches of the vagus nerve can technically be spared during minimally invasive transthoracic esophagectomy.<sup>18</sup> However, it is unclear, whether sparing these vagal nerve branches influences the inflammatory response and pulmonary function following esophagectomy. In this study, an experimental model was used to determine the effect of a bilateral cervical vagotomy on lipopolysaccharide (LPS) induced acute lung injury, the effect of selective sparing of the pulmonary branches of the vagus nerve on LPS-induced acute lung injury, and the role of the cholinergic anti-inflammatory pathway in this process.

## Materials & Methods

### Animals

Male Sprague Dawley rats, weighing 300 to 350 grams, purchased from Charles River Laboratories (Erkrath, Germany) were used. The rats were housed in a temperature- and humidity controlled room on a 12-hour light/dark cycle. Food and water were provided ad libitum. All animal experiments were conducted in compliance with the Guidelines of the Ethical Committee on the Use of Laboratory Animals of the Utrecht University.

### Surgical procedure and $\alpha 7$ nAChR stimulation

Forty-eight rats were anesthetized i.p. with urethane (10%, 2g/kg, U2500, Sigma-Aldrich, Zwijndrecht, The Netherlands) and randomized into 4 groups each consisting of 12 animals, according to the intervention. The sham group underwent a cervical and abdominal sham procedure; a small cervical midline incision was made and after division of the submaxillary glands and muscles the vagus nerve was identified bilaterally. Subsequently, rats were tracheotomized after which a tracheal cannula was placed and fixed with ligatures. After closing the cervical midline incision an abdominal midline laparotomy incision was made and both (anterior and posterior) subdiaphragmatic branches of the vagus nerve were identified after mobilisation of the left liver lobe, thereafter the abdomen was closed. The abdominal subdiaphragmatic vagotomy (AVGX) group underwent the same procedure, however, after identification of the abdominal vagus nerve both the posterior and anterior branch were transected subdiaphragmatically. This group models the preservation of the pulmonary branches of the vagus nerve. The cervical vagotomy (CVGX) group underwent the same procedure as the sham group, yet, after identification of the cervical vagus nerve it was transected bilaterally. This group models the transection of pulmonary branches. The last, cervical vagotomy plus GTS-21 (Sigma-Aldrich, Zwijndrecht, the Netherlands) (CVGX +  $\alpha 7$ nAChR-antagonist) group underwent the same procedure as the CVGX group. However, after closure of the abdominal incision GTS-21 (4 mg/kg, Sigma-Aldrich, Zwijndrecht, The Netherlands) was injected i.p. With this group, the hypothesis was tested that if any effects of a bilateral cervical vagotomy were observed, this was reversible through stimulation of the  $\alpha 7$ nAChR. Following surgery all rats received 0.05mg/kg lipopolysaccharide (LPS) (Sigma-Aldrich, Zwijndrecht, The Netherlands) intratracheally. In a pilot study, a dose-response with LPS was performed to find a dose of LPS that induced a profound reproducible influx of inflam-

matory cells into the airways (which was 0.05 mg/kg). Rectal temperature was monitored throughout the experiment and was kept between 36.5 °C and 37.5 °C using a heating pad and blankets. All rats underwent a pulmonary function test at 270 minutes and were euthanized 300 minutes after LPS administration by an overdose of i.p. injected pentobarbital (150 mg/kg) (Euthesate™, Ceva Santé Animale, Naaldwijk, The Netherlands). Pulmonary tissue, bronchoalveolar fluid (BALF), and blood samples were isolated and examined in accordance with the American Thoracic Society guidelines.<sup>19</sup>

### **Blockage of the $\alpha 7$ nAChR**

In a second experiment 24 rats were randomized into 3 groups (sham,  $\alpha 7$ nAChR-antagonist + sham,  $\alpha 7$ nAChR-antagonist + CVGX) of 8 animals and anesthetized (i.p. urethane, 10%, 2 g/kg, Sigma-Aldrich, Zwijndrecht, The Netherlands). The sham group underwent a cervical sham procedure, similar to the sham group of the first experimental protocol, however, this time no abdominal incision was made. The  $\alpha 7$ nAChR-antagonist + sham group received an  $\alpha 7$ nAChR-antagonist (Chlorisondamine diiodide, 0.125 mg/kg, Sigma-Aldrich, Zwijndrecht, the Netherlands) intravenously via the right internal jugular vein. After administration of the  $\alpha 7$ nAChR-antagonist a cervical sham procedure was performed. The  $\alpha 7$ nAChR-antagonist + CVGX group underwent the same procedure as the  $\alpha 7$ nAChR-antagonist group, but after the administration of the  $\alpha 7$ nAChR-antagonist a bilateral CVGX was performed. The perioperative protocol was similar to experimental protocol 1, however, to follow time dependent levels of cytokines in plasma, blood was withdrawn from the lateral tail vein pre-operatively, directly postoperative and 2 hours after LPS administration. A Flowchart of both experiments is depicted in Figure 1.



**Figure 1.** Time schedule experimental protocols

**Legend:** BW = Blood withdrawal. BW before the surgical procedure, after the surgical procedure and 2 hours after LPS was only carried out in the second experiment.

### Pulmonary Function Measurement

During the measurement of pulmonary function, all rats were placed in a temperature controlled plethysmograph (body temperature was kept at 37°C) in which they were ventilated (ventilation rate: 90 beats/min; volume 2ml/beat) and prepared for measuring pulmonary resistance (RL) and tidal volume (TV)). The previously placed tracheostomy was replaced by a small catheter that was connected to a pressure transducer fixed on the plethysmograph-box (EMKA Technologies, Paris, France) and transpulmonary pressure was determined by measuring pressure differences in the cannula in the trachea. Airflow and tidal volume were determined using a flow transducer fixed to the body box. Increasing doses of methacholine (acetyl- $\beta$ -methyl-choline chloride, Sigma-Aldrich, Zwijndrecht, The Netherlands) (0.37 - 50 mg/ml, 10% puff for 10 sec) were administered by aerosol generated in a nebulizer (EMKA Technologies, Paris, France) connected in between the plethysmograph and the ventilator (EMKA Technologies, Paris, France). After the first dose of methacholine pulmonary resistance was measured for 3 minutes, this procedure was repeated for all doses. Data were presented as average RL in cm H<sub>2</sub>O / (ml\*sec-1).

### Blood isolation

After rats were sacrificed blood samples were obtained by cardiac puncture. Twenty  $\mu$ l of blood was used to count the total numbers of leukocytes and a blood smear was made to determine the numbers of various white blood cells. The rest of the blood was centrifuged

(14000 g, Room Temperature, 5 min). Plasma was collected and samples were kept at -20°C until further analysis of TNF $\alpha$  and IL-6 levels.

### **Bronchoalveolar lavage**

After the rats were sacrificed, the thoracic cavity was opened and both lungs were taken out. The right main bronchus was cannulated and the right lungs were lavaged with 2 mL of pyrogen-free saline (0.9% NaCl, 37°C) supplemented with protease inhibitor cocktail tablet (Complete Mini, Roche Diagnostics, Mannheim, Germany). The supernatant of the first mL was used for cytokine measurement. Afterwards the right lung was lavaged 2 times with 2 mL saline solution (0.9% NaCl, 37°C). The BAL cells were centrifuged (300g, at 4°C, 5min) and pellets of the 3 lavages were pooled and total numbers of BAL cells were counted by use of a Bürker-Türk bright-line counting chamber (magnification 100x) (Karl Hecht Assistant KG, Sondheim/Rohm, Germany). For differential BAL cell counts cytopsin preparations were made and stained with Diff-Quick (Merz and Dade A.G., Düringen, Switzerland). After coding, all cytopsin preparations were evaluated by 2 independent observers using oil immersion microscopy (Leitz Optilux, Leica, Wetzlar, Germany). Numbers of macrophages, lymphocytes and neutrophils were scored by standard morphology. At least 200 cells per cytopsin preparation were counted and the absolute number of each cell type was calculated.<sup>20</sup>

### **Preparation of lung homogenates**

In brief, after lavage of the right lungs, the samples (150 mg/ml) were lysed on ice (by use of lysis buffer: 200 mM NaCl, 5 mM EDTA, 10 mM Tris, 10% glycerine, 1 mM PMSF, 1  $\mu$ g/ml leupeptin and 28  $\mu$ g/ml aprotinin (Sigma-Aldrich)) and homogenized. Then, the lung samples were centrifuged twice (1500 g at 4°C for 15 min) and supernatants were collected and stored at -20°C until further analysis of TNF $\alpha$  and IL-6 levels.

### **Lung histology**

The left lungs were fixed with 10% formalin infusion for 24h and thereafter embedded in paraffin after fixation, whereafter 5 $\mu$ m thick lung sections were cut (Leica, model RM2165, Germany) and stained with haematoxylin/eosin (H&E).<sup>21, 22</sup> Photomicrographs were taken with an Eclipse E800M microscope (Nikon Instruments Inc. The Netherlands) equipped with

a Nikon DXM 1200 digital Camera (Nikon Instruments Inc. the Netherlands). The LIS was determined in the H&E section according to the guidelines of the American Thoracic Society.<sup>19</sup> The esophagus, diaphragm, liver and stomach were resected en bloc and fixed in 10% formalin. The abdominal subdiaphragmatic vagotomy was confirmed in the specimen using acetylcholinesterase staining and by observing gastric dilatation during material harvesting.<sup>23</sup>

### **ELISA**

Both IL-6 (BMS625) and TNF- $\alpha$  (BMS622) were measured in plasma, BALF or lung homogenates with a Ready-SET-Go!® ELISA kit (eBioscience, San Diego, California, USA). The concentrations of these cytokines were expressed as pg/ml.

### **Statistics**

Data were analyzed using SPSS for windows, version 22.0 (IBM corp., Armonk, New York). Data were tested for normal distribution with the Kolmogorov-Smirnov test. Statistical differences between groups were studied by one-way anova with post-hoc Dunns comparison when the data were normally distributed. To specifically zoom in on differences between two groups the unpaired t test was used. When the data was not normally distributed the statistical differences between groups were detected by Kruskal Wallis. Mann Whitney U-test was used for analysis between groups. All data was expressed as mean  $\pm$  standard error. A *p*-value of < 0,05 was considered statistically significant.



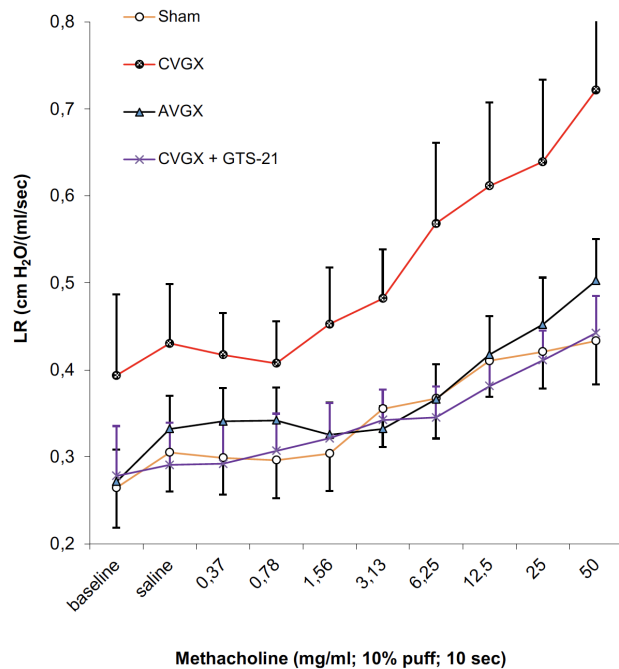
## Results

### Bilateral cervical vagotomy aggravates LPS-induced lung injury

When compared to a sham procedure, a bilateral cervical vagotomy resulted in a substantial deterioration of pulmonary function; both the pulmonary resistance ( $0.723 \pm 0.242$  cm H<sub>2</sub>O/(ml/sec) vs.  $0.444 \pm 0.157$  cm H<sub>2</sub>O/(ml/sec);  $P=0.007$ ) (Figure 2) and the Lung Injury Score (LIS) ( $0.397 \pm 0.092$  (CVGX) vs.  $0.159 \pm 0.110$  (sham);  $P=0.016$ ) (Figure 3) were significantly increased. There was a significant increase in macrophages ( $10^4$ ) ( $136 \pm 76$  (CVGX) vs.  $64 \pm 39$  (sham);  $P=0.023$ ) and lymphocytes ( $10^4$ ) (range) ( $17$  (0-40) (CVGX) vs.  $9$  (0-48) (sham);  $P=0.036$ ) in the BALF. Furthermore, also the total number of cells ( $10^5$ , plasma) ( $136 \pm 43$  (CVGX) vs.  $112 \pm 35$  (sham);  $P=0.044$ ), and total number of mononuclear cells ( $10^5$ , plasma) (range) ( $31$  (9-68) (CVGX) vs.  $20$  (15-35) (sham);  $P=0.036$ ) were significantly increased in the CVGX group. Neutrophils in BALF were not statistically significant affected by cervical vagotomy neither was the number of polymorphic cells in plasma (Figure 4). As demonstrated in figure 5, both the levels of TNF- $\alpha$  and IL-6 in pulmonary homogenates were not significantly higher after a bilateral cervical vagotomy when compared to the sham group.

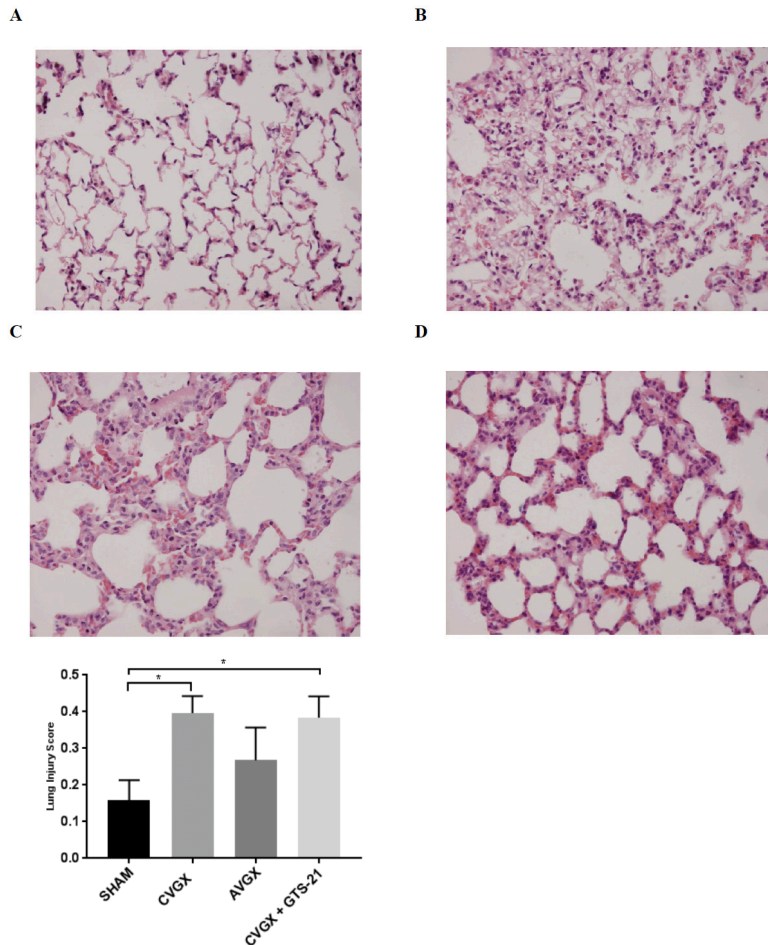
### Selective sparing of pulmonary vagus nerves reduces LPS-induced lung injury

Compared to the CVGX group, pulmonary resistance ( $0.723 \pm 0.242$  cm H<sub>2</sub>O/(ml/sec) vs.  $0.501 \pm 0.146$  cm H<sub>2</sub>O/(ml/sec);  $P=0.040$ ) (Figure 2) was significantly reduced in the AVGX group. The LIS was not statistically significant affected ( $0.397 \pm 0.092$  (CVGX) vs.  $0.268 \pm 0.179$  (AVGX)  $P=0.248$ ). Furthermore, both the number of macrophages ( $10^4$ , BALF) ( $136 \pm 76$  vs.  $71 \pm 39$ ;  $P=0.027$ ) and total number of cells ( $10^5$ , plasma) ( $136 \pm 43$  vs.  $115 \pm 22$ ;  $P=0.034$ ) were reduced in the AVGX group. The other inflammatory cells BALF and blood also showed a decreased tendency in the AVGX group (Figure 4). No significant differences between the AVGX group and the CVGX group were found in the levels of both TNF- $\alpha$  and IL-6 in pulmonary homogenates (Figure 5). Notably, between the AVGX and sham group, none of the outcome measures were significantly different.



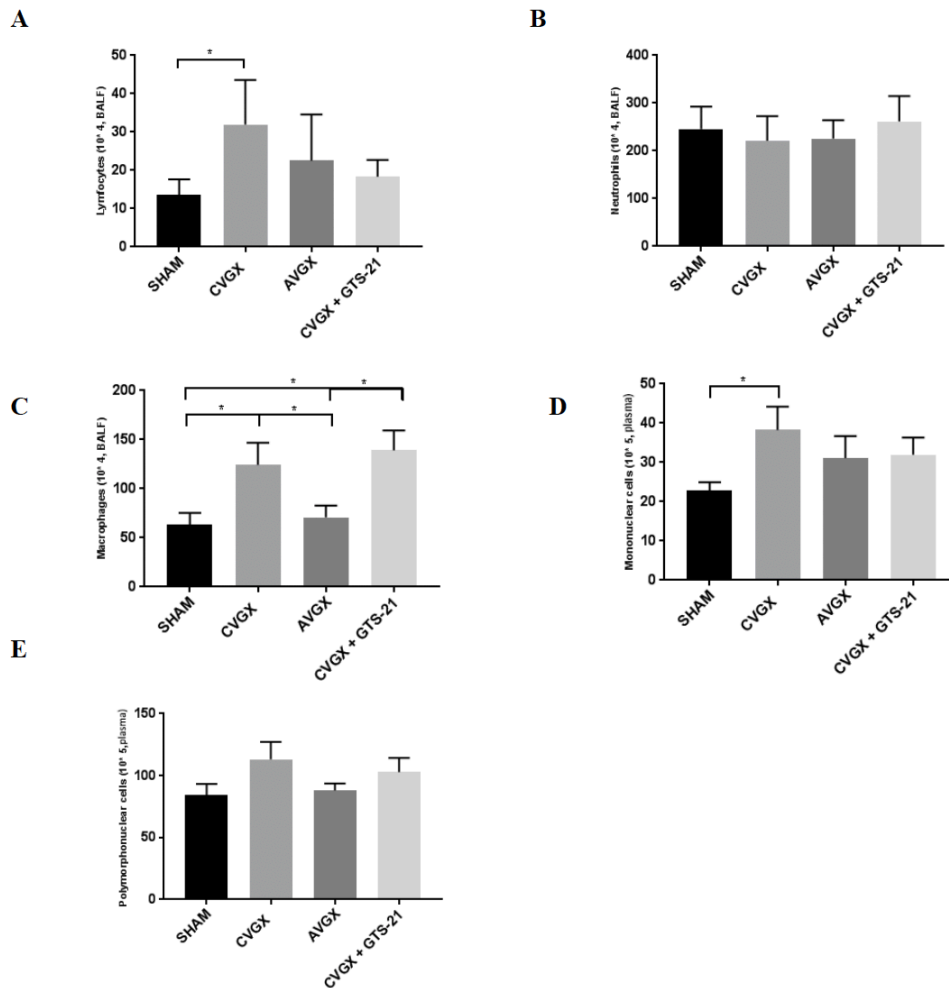
**Figure 2. Pulmonary resistance** Bilateral cervical vagotomy significantly increased pulmonary resistance when compared to the AVGX- ( $p=0.040$ ) and sham- ( $P=0.007$ ) group, this effect was nullified after administration of GTS-21. Data are represented as mean  $\pm$  SEM.  $N = 12$  rats per group. Statistical analysis was performed using one-way anova with post-hoc Dunns comparison between the individual groups.

**Abbreviations:** LR = Lung Resistance; CVGX= Cervical vagotomy, AVGX = Abdominal vagotomy.



**Figure 3: Lung morphology** Representative histological sections of the lungs were stained with H&E at x400 magnification **A:** In the sham group the alveolar walls are relatively thin and the alveoli contain occasional alveolar macrophages. **B and C:** In the CVGX group and the CVG the alveolar walls are thickened with intramural macrophages and neutrophils. Furthermore, some hyaline membranes and proteinaceous debris filling the airspaces may be observed **D:** The AVGX group shows somewhat thickened alveolar walls infiltrated with macrophages and neutrophils. **E:** Bar charts of the differences in lung injury score. CVGX significantly increased the LIS ( $P=0.016$ ). Data are represented as mean  $\pm$  SEM. \*indicates  $p<0.05$ .  $N = 12$  rats per group. Statistical analysis was performed using one-way anova with post-hoc Dunns comparison between the individual groups.

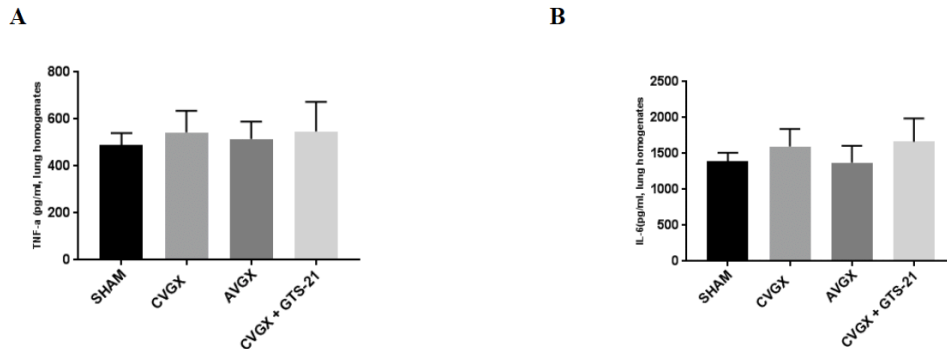
**Abbreviations:** CVGX= Cervical vagotomy, AVGX = Abdominal vagotomy.



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**Figure 4: Number of cells in BALF and plasma.** Bilateral cervical vagotomy resulted in a significant increase in lymphocytes (A) ( $P=0.036$ ) and macrophages (C) ( $P=0.023$ ) in the BALF when compared to the sham group. These numbers were reduced (lymphocytes:  $P=0.080$ , macrophages:  $P=0.027$ ) in the AVGX group when compared to the CVGX group. The number of mononuclear cells (D) ( $P=0.037$ ) in the plasma was significantly increased after bilateral cervical vagotomy. Polymorphic cells in plasma were not statistically significantly affected by cervical vagotomy (E) ( $P=0.097$ ). Data are represented as mean  $\pm$  SEM. \* indicates  $p < 0.05$ .  $N = 12$  rats per group. Statistical analysis was performed using one-way anova with post-hoc Dunns comparison between the individual groups.

**Abbreviations:** CVGX = Cervical vagotomy, AVGX = Abdominal vagotomy.



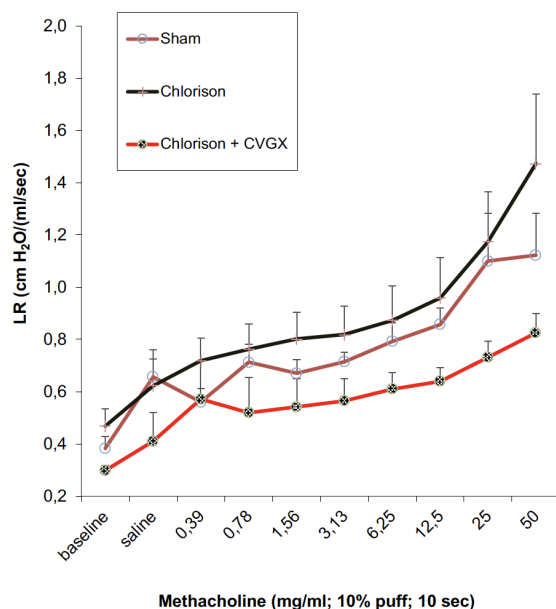
**Figure 5: TNF- $\alpha$  and IL-6 in lung homogenates.** No significant differences in levels of TNF- $\alpha$  and IL-6 in the BALF between groups were demonstrated. Data are represented as mean  $\pm$  SEM.

**Legend:** CVGX= Cervical vagotomy, AVGX = Abdominal vagotomy.  $N = 12$  rats per group. Statistical analysis was performed using one-way anova. **Abbreviations:** CVGX= Cervical vagotomy, AVGX = Abdominal vagotomy.

### Role of $\alpha 7$ nAChR in acute lung injury after bilateral cervical vagotomy

Rats that underwent cervical vagotomy (CVGX) were divided in a group that received a  $\alpha 7$ nAChR-agonist and a group that did not receive a  $\alpha 7$ nAChR-agonist. Interestingly, the  $\alpha 7$ nAChR-agonist nullified the increase in pulmonary resistance in CVGX-treated animals ( $0.723 \pm 0.242$  cm H<sub>2</sub>O/(ml/sec) vs.  $0.407 \pm 0.136$  cm H<sub>2</sub>O/(ml/sec);  $P=0.007$ ) (Figure 2) In contrast, there was no effect on LIS (Figure 3). Moreover, there were no significant differences between the CVGX group and the CVGX +  $\alpha 7$ nAChR-agonist group in lymphocytes, neutrophils and macrophages in BALF and mononuclear and polymorphic cells in plasma (Figure 4). No changes in both TNF- $\alpha$  and IL-6 in pulmonary homogenates were observed (Figure 5).

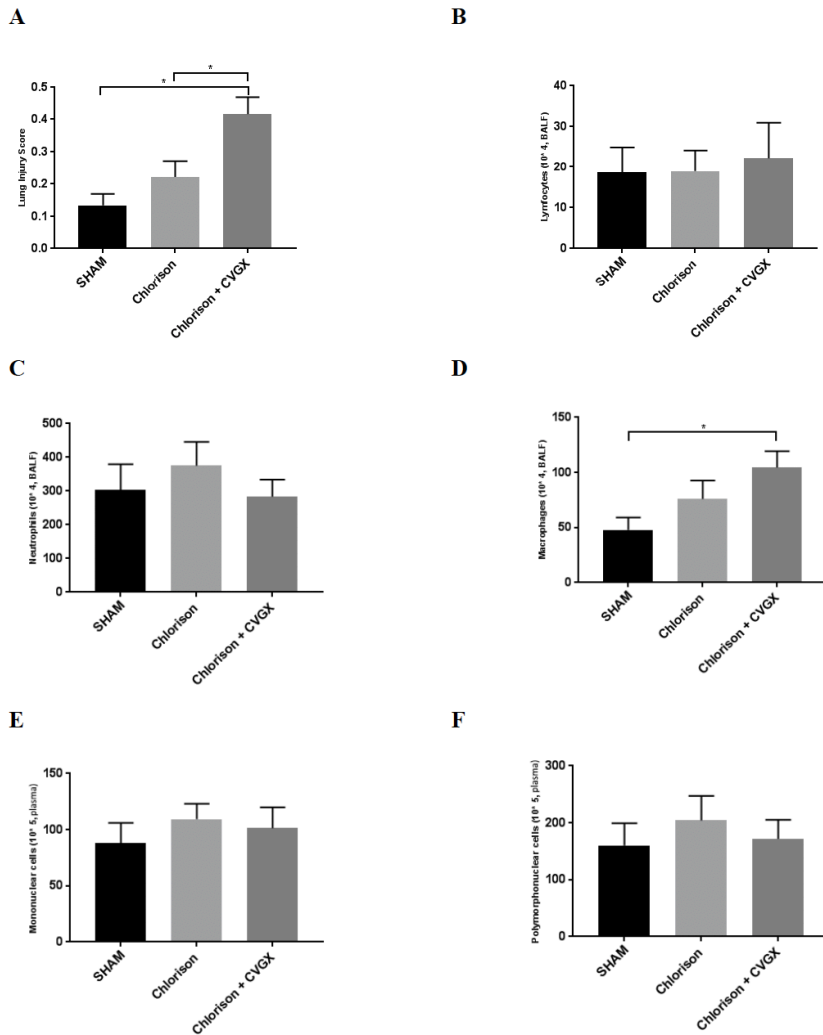
Administration of a  $\alpha 7$ nAChR-antagonist did not significantly increase pulmonary resistance (Figure 6), and LIS when compared to a group that underwent a cervical sham procedure (Figure 7). Also, leukocytes in BALF and both the mononuclear and polymorphic cells in plasma, were not significantly increased after  $\alpha 7$ nAChR-antagonist administration (Figure 7). Furthermore, there were no significant differences between groups in TNF- $\alpha$  in both BALF and plasma, and a possible curve of cytokine levels in the plasma could not be demonstrated in the current study. As demonstrated in figure 7 the LIS and all types of cells in both BALF and plasma were slightly increased after administration of an  $\alpha 7$ nAChR-antagonist, however not statistically significant.



**Figure 6: Pulmonary Resistance.** The administration of Chlorisondamine diiodide increased pulmonary resistance, however this increase was not statistically significant. Due to the severe histopathological injury in the group that underwent a bilateral cervical vagotomy after administration of Chlorisondamine diiodide no reliable assessment of pulmonary resistance could be made. Data are represented as mean  $\pm$  SEM. N = 8 rats per group.

**Abbreviations:** LR = Lung Resistance; CVGX= Cervical vagotomy.

To validate whether a bilateral cervical vagotomy aggravates LPS-induced acute lung injury in the presence of intravenously administrated  $\alpha 7$ nAChR-antagonist, the outcomes of the  $\alpha 7$ nAChR-antagonist + sham group were compared with the outcomes of the  $\alpha 7$ nAChR-antagonist + CVGX group. The LIS increased tremendously in the  $\alpha 7$ nAChR-antagonist + CVGX group ( $0.134 \pm 0.098$  vs.  $0.416 \pm 0.154$ ;  $P=0.002$ ) (Figure 7). Furthermore, 2 (25%) out of 8 rats died 4 hours after LPS-administration due to exhaustion. The severe histological pulmonary injury resulted in the impossibility to reliably conduct and assess a pulmonary function test (figure 6). Differences in TNF- $\alpha$  in both BALF and plasma could not be demonstrated on all moments of measurement (figure 8).

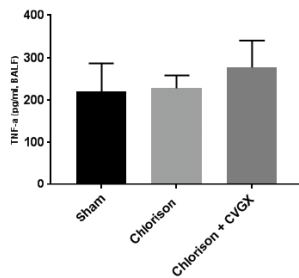


**Figure 7. Bar charts of the differences in LIS (A) and number of cells in BALF and plasma (B-F).** LIS increased statistically significant when a bilateral cervical vagotomy was performed after administration of Chlorisondamine diiodide ( $P=0.002$ ) (A). Furthermore, the number of macrophages in BALF(D) was statistically significant increased in the Chlorison + CVGX group ( $P=0.015$ ). \* indicates  $p<0.05$ .  $N = 8$  rats per group. Statistical analysis was performed using one-way anova with post-hoc Dunns comparison between the individual groups.

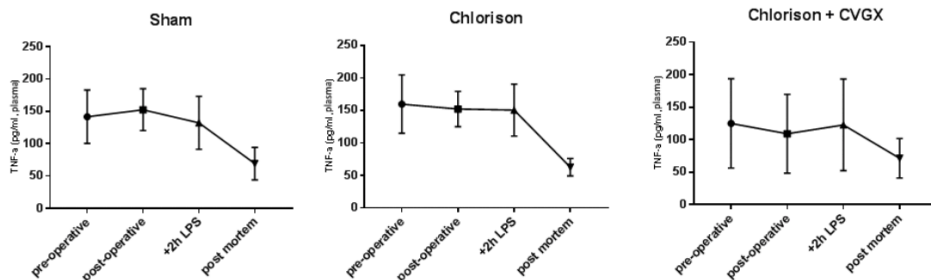
**Abbreviations:** CVGX= Cervical vagotomy

All leukocytes in BALF, and both mononuclear and polymorphic cells in plasma, were not statistically significant increased when a bilateral cervical vagotomy instead of a sham procedure was performed after the administration of a  $\alpha 7$ nAChR-antagonist. However, when the  $\alpha 7$ nAChR-antagonist + CVGX group was compared with the sham group local macrophages were, besides LIS ( $0.415 \pm 0.154$  vs.  $0.135 \pm 0.098$ ;  $P=0.002$ ), statistically significant increased (BALF,  $10^4$ ) ( $47.8 \pm 31.9$  vs.  $104.5 \pm 41.9$ ;  $P=0.015$ ).

A



B



**Figure 8: TNF- $\alpha$  in lung homogenates.** No statistically significant differences in the levels of TNF- $\alpha$  and the BALF and in plasma over time could be demonstrated between groups. Data are represented as mean  $\pm$  SEM. N = 12 rats per group. Statistical analysis was performed using one-way anova.

**Abbreviations:** CVGX= Cervical vagotomy



## Discussion

In the present study, it was demonstrated that a bilateral cervical vagotomy results in a substantial deterioration of pulmonary function in LPS-induced acute lung injury. Instead, a subdiaphragmatic abdominal vagotomy did not exert this effect indicating that pulmonary branches of the vagus nerve have an important function during LPS-induced acute lung injury.

It was demonstrated that the aggravation of LPS-induced acute lung injury after bilateral cervical vagotomy is not solely mediated by the  $\alpha 7$ nAChR. This indicates that also other pathways mediated by the vagus nerve regulate severity of LPS-induced acute lung injury. The respiratory system is densely innervated by vagal sensory nerve fibers that regulate several autonomic functions, such as mucosal mast cell activation, mucus secretion, the breathing pattern, bronchospasm and possibly inflammation.<sup>24,25,26</sup> Loss of each of these functions may contribute to an increase pulmonary injury.

Another autonomic function which ceases to exist after bilateral cervical vagotomy is the so-called Hering-Breuer reflex.<sup>27</sup> Pulmonary stretch receptors are substantially innervated by the vagus nerve and play an important role in the mediation of information on pulmonary mechanics. Inspiratory and expiratory time are influenced by these receptors in response to changes in airflow and transpulmonary pressure. The inhibition of further inspiration of air when the lungs are inflated is called the Hering-Breuer reflex.<sup>28</sup> It was recently demonstrated that inhibition of afferent vagus nerve signaling resulted in increased tidal volume.<sup>29</sup> In the present experiment the pulmonary stretch receptor-feedback was abolished due to the bilateral cervical vagotomy. This could have led to harmful tidal volumes and pulmonary injury.

Remarkably, a strong respiratory depression and an increase in inspiratory and expiratory time was observed in the current experiments. These results are in line with a recently published study, in which a clearly noticeable change in breathing pattern was observed after bilateral cervical vagotomy. Furthermore, an increase in pulmonary inflammation in bilateral cervical vagotomized spontaneously breathing rats was demonstrated, while bilateral cervical vagotomized mechanical ventilated (tidal volume is set) rats did not show an increased pulmonary inflammation.<sup>30</sup>

Since the cholinergic anti-inflammatory pathway was a likely pathway that would be affected in this model by vagotomy, the role of the  $\alpha 7$ nAChR was studied. Borovikova et al.<sup>31</sup> showed that acetylcholine released from stimulated cholinergic nerves activate the  $\alpha 7$ nAChR on tissue resident macrophages, reducing the release of pro-inflammatory cytokines.<sup>31</sup> In contrast to the findings on histological lung injury, pulmonary function and leukocyte levels in both BALF and plasma, TNF- $\alpha$  and IL-6 levels after bilateral cervical vagotomy was not increased. Although it could not be detected, there may very well have been an increase in cytokine levels after bilateral cervical vagotomy, since there were more lymphocytes and macrophages in the BALF and even more mononuclear cells systemically. This may be due to the moment of measurement. In this second experiment, it was attempted to demonstrate a possible curve by measurements at additional time-points (pre-operative, postoperative, and 2 hours after LPS administration), however still no differences between groups were observed in blood. This implies that the role of cytokines was limited or that the peak concentration of cytokines came even earlier in the current experiments.

It was suggested by Rosas-Ballina et al.<sup>32</sup> that an adequate spleen function is pivotal in the cholinergic anti-inflammatory pathway. They showed that vagus nerve stimulation during sepsis specifically reduces the production of cytokines by splenic macrophages. Although the spleen is not innervated by cholinergic nerve fibers, it is thought to be stimulated by the vagus nerve through the celiac-superior mesenteric ganglion complex.<sup>32</sup> Through this mechanism the splenic nerve gets activated and releases norepinephrine, directly reducing cytokine production in splenic macrophages.

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Another pathway that reduces cytokine production by splenic nerve released norepinephrine is the enhancement of splenic acetylcholine through acetylcholine-synthesizing T-cells.<sup>33</sup> Matteoli et al.<sup>34</sup> demonstrated that the cholinergic anti-inflammatory pathway also directly stimulates tissue resident macrophages expressing  $\alpha 7$ nAChR. In their study, stimulation of the vagus nerve in animals devoid of splenic innervation still reduced intestinal inflammation.<sup>34</sup> The latter is in line with the outcomes of the present study in which a subdiaphragmatic vagotomy, that eliminated involvement of the celiac-superior mesenteric ganglion complex, did not aggravate lung injury while a bilateral cervical vagotomy did. Nevertheless, it was

demonstrated that the role of the cholinergic anti-inflammatory pathway is limited in LPS-induced acute lung injury, which also may be an explanation for the little effect of a subdiaphragmatic vagotomy.

As discussed above, both the  $\alpha 7$ nAChR-antagonist and the  $\alpha 7$ nAChR-agonist did not significantly affect LPS-induced acute lung injury. However, administration of GTS-21 after bilateral cervical vagotomy did nullify the increased pulmonary resistance. Although GTS-21 is a specific  $\alpha 7$ nAChR-agonist,  $\alpha 7$ nAChR are present on many cells, for example on tracheal smooth muscle cells.<sup>35,36</sup> Due to i.p. administration of GTS-21 a significant share of these cells could have been activated through their  $\alpha 7$ nAChRs. This may have caused relaxation of tracheal smooth muscle cells, resulting in a decrease of measured pulmonary resistance. Likewise, Chlorisondamine diiodide might have caused contraction of tracheal smooth muscle cells.

The results of the current study indicate that there is an important role for the autonomic function of the vagus nerve in LPS-induced acute lung injury. Stimulation of the vagus nerve has an inhibitory effect on the production of mucosal mast cells through the  $\alpha 7$ nAChR.<sup>24</sup> Taking this into account, a vagotomy may aggravate lung injury through the upregulation of mucosal mast cells. Furthermore, when pulmonary C-fibers are stimulated, the vagus nerve reflexively increase the secretion of mucus by tracheal submucosal glands.<sup>37</sup> An increased presence of mucus may reduce pulmonary function by obstructing the bronchial lumen, on the contrary it enhances the primary barrier against foreign antigens.

In conclusion, the current data indicate that the vagus nerve is an important mediator in development of acute lung injury in a LPS-induced sepsis model. The effects seem to be specific for the vagus nerve and were not dependent on activation or suppression of the cholinergic anti-inflammatory pathway. Sparing or targeted stimulation of vagus nerve fibres during surgery may be a therapeutic procedure to reduce pulmonary complications after transthoracic esophagectomy. The exact downstream pathway underlying the observed effects of vagotomy needs further investigation.

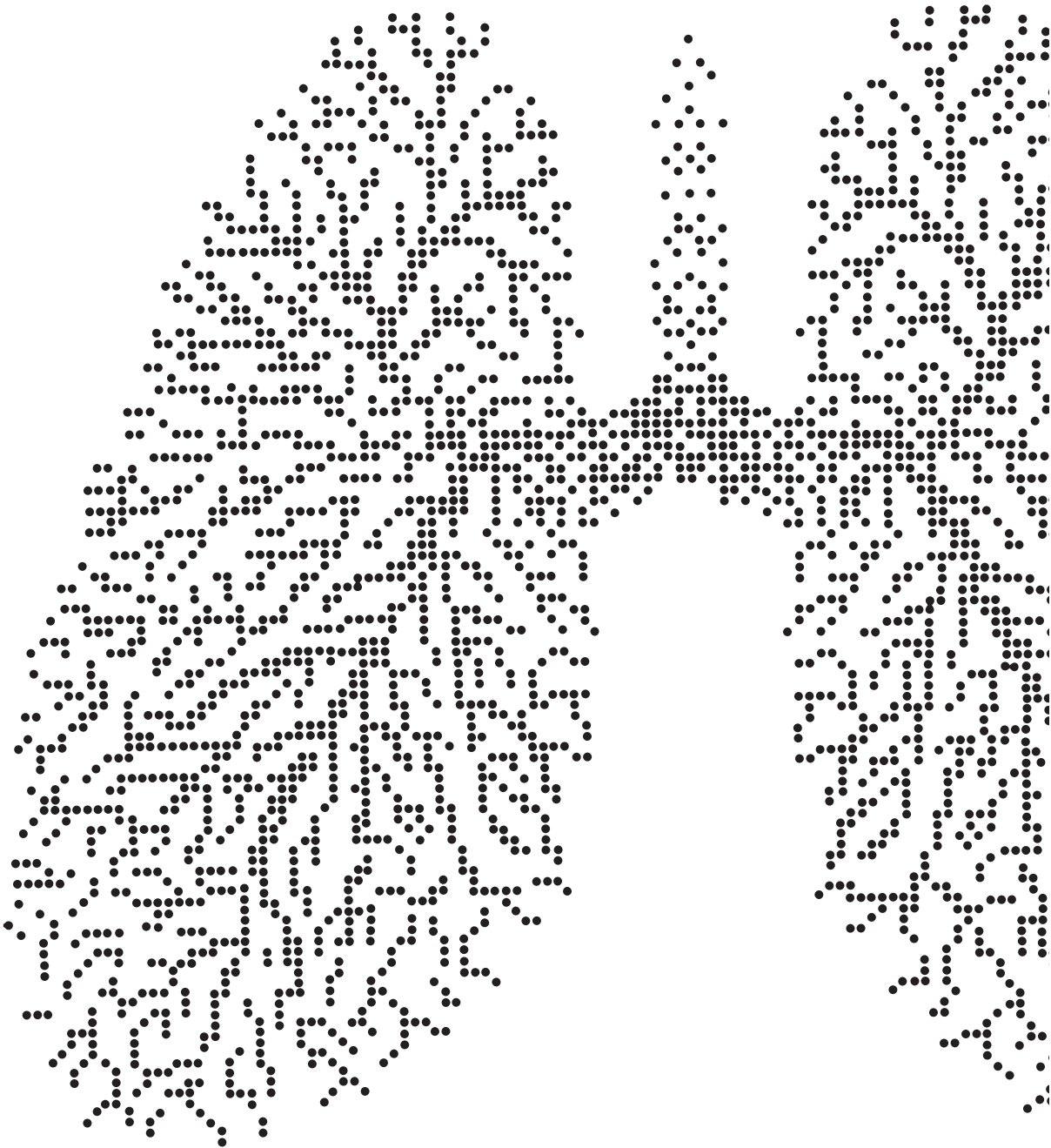
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# Chapter 12

## High-fat enteral nutrition reduces LPS-induced acute lung injury

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## Abstract

**Introduction:** An increased inflammatory response has been demonstrated to independently predict the occurrence of pulmonary complications after esophagectomy. High-fat enteral nutrition activates humoral and neural pathways which may attenuate lung inflammation and prevent organ injury. The aim of the current study was to determine the effect of high-fat enteral nutrition on lipopolysaccharide (LPS) induced acute lung injury

**Methods:** Male rats (N=24) were divided into three groups (N=8): Sham procedure after fasting (FS), sham procedure after high-fat enteral nutrition (HFS) and abdominal vagotomy after high-fat enteral nutrition (HFV). All rats were administered LPS intratracheally following vagotomy. After 270 minutes a pulmonary function test was conducted and directly afterwards all rats were sacrificed to assess parameters of systemic inflammation and organ injury.

**Results:** Administration of high-fat nutrition reduced LPS-induced histopathological lung injury (Lung Injury Score (LIS):  $0.600 \pm 0.067$  (FS) vs.  $0.307 \pm 0.053$  (HFS);  $P=0.004$ ). This effect remained after an abdominal vagotomy (LIS:  $0.307 \pm 0.053$  (HFS) vs.  $0.275 \pm 0.028$  (HFV);  $P=0.613$ ). Additionally, an abdominal vagotomy increased pulmonary resistance ( $0.663 \pm 0.092$  cm H<sub>2</sub>O/(ml/sec) (HFS) vs.  $0.911 \pm 0.084$  H<sub>2</sub>O/(ml/sec) (HFV);  $P=0.040$ ) and decreased the dynamic compliance  $0.178 \pm 0.037$  H<sub>2</sub>O/(ml/sec) (HFS) vs.  $0.080 \pm 0.012$  H<sub>2</sub>O/(ml/sec) (HFV);  $P<0.001$ ). There were no statistical significant differences in cytokine- and leukocyte levels in both bronchoalveolar lavage fluid and plasma.

**Conclusions:** Preoperative administration of high-fat enteral nutrition reduces LPS-induced acute lung injury. These effects seem to be not only specific for the vagus nerve. This makes a preoperative dietary intervention translational to the clinic, potentially offering a therapeutic window to reduce the severity pulmonary complications after esophagectomy.

## Introduction

Esophagectomy is a central component of multimodality treatment for resectable gastro-esophageal junction- and esophageal cancer.<sup>1,2</sup> It is a highly complex procedure, which is frequently followed by pulmonary complications. These complications are associated with an increased intensive care unit readmission rate, length of hospital stay, and mortality.<sup>3,4</sup> Although many factors have been associated with the occurrence of pulmonary complications, an increased inflammatory response has been demonstrated to independently predict their occurrence.<sup>5</sup> The vagus nerve exerts an important regulatory role in inflammation and many other pulmonary functions.<sup>6-9</sup> Recently, we have demonstrated that sparing the pulmonary branches of the vagus nerve without compromising a radical lymphadenectomy is feasible during minimally invasive transthoracic esophagectomy.<sup>10,11</sup> Sparing the pulmonary branches of the vagus nerve reduces LPS-induced acute lung injury in an experimental setting. Stimulation of these nerve branches may further reduce LPS-induced acute lung injury.<sup>8,12</sup> This might be achieved through high-fat nutrition.<sup>13-18</sup> Enteral administration of high-fat nutrition activates the autonomic nervous system through cholecystokinin (CCK) receptors on the afferent vagus nerve. Subsequently, nicotinic receptors on local inflammatory cells are activated via the efferent vagus nerve, which leads to a reduced cytokine release and less organ damage.<sup>13,15</sup> Therefore we hypothesize that administration of high-fat enteral nutrition before esophagectomy may reduce postoperative pulmonary complications. The aim of this study was to investigate the effects of high-fat nutrition on LPS-induced acute lung injury. Additionally, vagus nerve involvement in the immune-modulating effect of high-fat enteral nutrition was determined.

## Methods

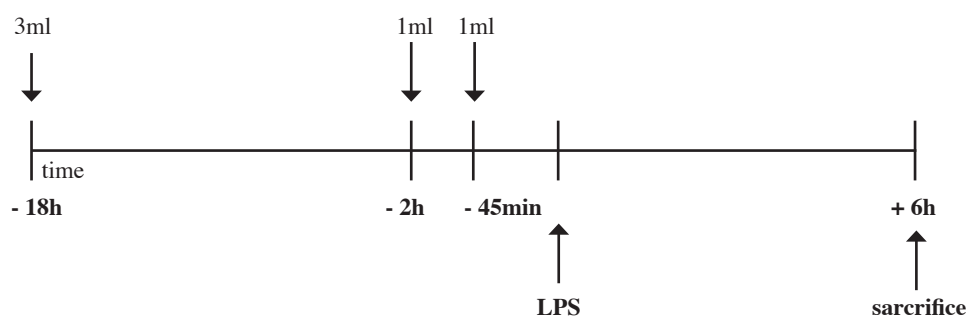
### Animals

Male Sprague Dawley rats (300 to 350 grams) were purchased from Charles River Laboratories. The rats were housed in a temperature- and humidity controlled room on a 12-hour light/dark cycle. All animal experiments were conducted in compliance with the Guidelines of the Ethical Committee on the Use of Laboratory Animals of the Utrecht University.

### High-fat enteral feeding and surgical procedure

After induction of anesthesia with urethane i.p. (10%, 2g/kg, U2500, Sigma-Aldrich, Zwijndrecht, The Netherlands) 24 rats were randomized into 3 groups of 8 animals, according to the intervention. The fasting sham (FS) group was fasted for 18 hours and underwent an abdominal sham procedure; a midline laparotomy incision was made and after mobilisation of the left liver lobe, both the anterior and posterior subdiaphragmatic branches of the vagus nerve were identified, thereafter the abdomen was closed. The other two groups received high-fat enteral nutrition according to the schema as depicted in Figure 1. The high-fat enteral feeding + sham procedure (HFS) group underwent the same surgical procedure as the FS group. The high-fat enteral feeding + vagotomy (HFV) group underwent the same surgical procedure as the other two groups, however, after identification of the abdominal vagus nerve both the posterior and anterior branch were transected subdiaphragmatically. The high-fat nutrition contained 50.4 energy percent (en%) fat (30 en% are phospholipids), 8.7 en% protein, and 40.9 en% carbohydrates. The lipid source was soy lecithin. Omega-3 and omega-6 fatty acids constituted less than 5 wt% (<5 g/100mL). Proteins were derived from lean milk powder containing 80% casein and 20% whey protein. The source for carbohydrates was a mixture of sucrose and maltodextrins. Following surgery all rats were tracheotomized after which a tracheal cannula was placed and fixed with ligatures. Directly afterwards all rats received 0.05 mg/kg lipopolysaccharide (LPS) (Sigma-Aldrich, Zwijndrecht, The Netherlands) intratracheally. Rectal temperature was monitored throughout the experiment and was kept between 36.5 °C and 37.5 °C using a heating pad and blankets. All rats underwent a pulmonary function test at 270 minutes and were euthanized 300 minutes after LPS administration by an overdose of i.p. injected pentobarbital (150 mg/kg) (Euthesate™, Ceva Santé Animale, Naaldwijk, The Netherlands). In accordance with the American Thoracic Society guidelines, pulmonary tissue, bronchoalveolar fluid (BALF), and blood samples were

isolated and examined.<sup>19</sup>



**Figure 1. Feeding schedule.** At T = -18 hours, rats were starved overnight. At T = -18 hours the HFS and HFV groups received an oral gavage of 3ml high-fat nutrition and at T = -2 hours and T = -45 minutes the HFS and HFV groups received another oral gavage of 1 ml of high-fat nutrition. At T = 0, directly after surgery, all rats received 0.05mg/kg LPS intratracheally.

**Abbreviations:** HFS: High-Fat Sham, HFV: High-Fat Vagotomy, LPS: Lipopolysaccharide.

### Pulmonary Function Measurement

All rats were placed in a temperature controlled plethysmograph (body temperature was kept at 37°C) in which they were ventilated (ventilation rate: 90 beats/min; volume 2ml/beat) and prepared for measuring pulmonary resistance (RL) and tidal volume (TV). The previously placed tracheostomy was replaced by a small catheter and connected to a pressure transducer fixed on the plethysmographbox (EMKA Technologies, Paris, France). Transpulmonary pressure was determined by measuring pressure differences in the cannula in the trachea. A flow transducer fixed to the body box was used to measure airflow and tidal volume. Increasing doses of methacholine (acetyl- $\beta$ -methyl-choline chloride, Sigma-Aldrich, Zwijndrecht, The Netherlands) (0.37 - 50 mg/ml, 10% puff for 10 sec) were administered by aerosol generated in a nebulizer (EMKA Technologies, Paris, France) connected in between the plethysmograph and the ventilator (EMKA Technologies, Paris, France). After the first dose of methacholine pulmonary resistance was measured for 3 minutes, this procedure was repeated for all doses. Data were presented as average RL in cm H<sub>2</sub>O / (ml\*sec-1).

### **Blood isolation**

Directly before and after surgery, and two hours after LPS-administration, 0.5 ml blood samples were obtained through lateral tail vein puncture. After rats were sacrificed blood samples were obtained by cardiac puncture. Twenty  $\mu$ l of blood was used to count the total numbers of leukocytes and a blood smear was made to determine the numbers of various white blood cells. The rest of the blood was centrifuged (14000 g, Room Temperature, 5 min). Plasma was collected and samples were kept at -20°C until further analysis of cytokines.

### **Bronchoalveolar lavage**

After the rats were sacrificed, the thoracic cavity was opened and both lungs were taken out. The right main bronchus was cannulated and the right lungs were lavaged with 2 mL of pyrogen-free saline (0.9% NaCl, 37°C) supplemented with protease inhibitor cocktail tablet (Complete Mini, Roche Diagnostics, Mannheim, Germany). The supernatant of the first mL was used for cytokine measurement. Afterwards the right lung was lavaged 2 times with 2 mL saline solution (0.9% NaCl, 37°C). The BALF cells were centrifuged (300g, at 4°C, 5min) and pellets of the 3 lavages were pooled and total numbers of BALF cells were counted by use of a Bürker-Türk bright-line counting chamber (magnification 100x) (Karl Hecht Assistant KG, Sondheim/Rohm, Germany). For differential BALF cell counts cytopsin preparations were made and stained with Diff-Quick (Merz and Dade A.G., Dürdingen, Switzerland). After coding, all cytopsin preparations were evaluated by 2 independent observers using oil immersion microscopy (Leitz Optilux, Leica, Wetzlar, Germany). Numbers of macrophages, lymphocytes and neutrophils were scored by standard morphology. At least 200 cells per cytopsin preparation were counted and the absolute number of each cell type was calculated.<sup>20</sup>

### **Preparation of lung homogenates**

In brief, after lavage of the right lungs, the samples (150 mg/ml) were lysed on ice (by use of lysis buffer: 200 mM NaCl, 5 mM EDTA, 10 mM Tris, 10% glycerine, 1 mM PMSF, 1  $\mu$ g/ml leupeptin and 28  $\mu$ g/ml aprotinin (Sigma-Aldrich)) and homogenized. Then, the lung samples were centrifuged twice (1500 g at 4°C for 15 min) and supernatants were collected and stored at -20°C until further analysis of TNF $\alpha$  and IL-6 levels.

### **Lung histology**

The left lungs were fixed with 10% formalin infusion for 24h and thereafter embedded in paraffin after fixation, whereafter 5µm thick lung sections were cut (Leica, model RM2165, Germany) and stained with haematoxylin/eosin (H&E).<sup>21, 22</sup> Photomicrographs were taken with an Eclipse E800M microscope (Nikon Instruments Inc. The Netherlands) equipped with a Nikon DXM 1200 digital Camera (Nikon Instruments Inc. the Netherlands). The Lung Injury Score (LIS) was determined in the H&E section according to the guidelines of the American Thoracic Society.<sup>19</sup>

### **ELISA**

Both IL-6 (BMS625) and TNF- $\alpha$  (BMS622) were measured in plasma and lung homogenates with a Ready-SET-Go!® ELISA kit (eBioscience, San Diego, California, USA). The concentrations of these cytokines were expressed as pg/ml.

### **Statistics**

Data were analyzed using SPSS for windows, version 22.0 (IBM corp., Armonk, New York). Data were tested for normal distribution with the Kolmogorov-Smirnov test. Statistical differences between groups were studied by one-way anova with post-hoc Dunns comparison when the data were normally distributed. To specifically zoom in on differences between two groups the unpaired t test was used. When the data was not normally distributed the statistical differences between groups were detected by Kruskal Wallis. Mann Whitney U-test was used for analysis between groups. All data was expressed as mean  $\pm$  standard error. A *p*-value of  $< 0,05$  was considered statistically significant.

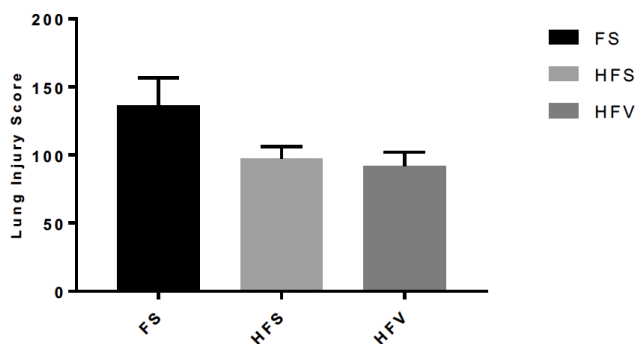
## Results

### High-fat nutrition reduces LPS-induced histopathological lung injury

Preoperative administration of high-fat enteral nutrition resulted in a significant reduction in LIS ( $0.600 \pm 0.067$  (FS) vs.  $0.307 \pm 0.053$  (HFS);  $P=0.004$ ). (Figure 2) Both the pulmonary resistance ( $0.616 \pm 0.112$  cm H<sub>2</sub>O/(ml/sec) (FS) vs.  $0.663 \pm 0.092$  cm H<sub>2</sub>O/(ml/sec) (HFS);  $P=0.757$ ) and the dynamic compliance ( $0.218 \pm 0.087$  cm H<sub>2</sub>O/(ml/sec) (FS) vs.  $0.178 \pm 0.037$  H<sub>2</sub>O/(ml/sec) (HFS);  $P=0.270$ ) were not statistically significant affected by preoperative administration of high-fat enteral nutrition. (Figure 3) Also the total number of macrophages ( $39 \pm 7$  (FS) vs.  $44 \pm 9$  (HFS);  $P=0.721$ ), neutrophils ( $129 \pm 15$  (FS) vs.  $139 \pm 13$  (HFS);  $P=0.645$ , and lymphocytes  $7 \pm 2$  (FS) vs.  $8 \pm 2$  (HFS);  $P=0.878$ ) in the BALF were not affected by high-fat enteral nutrition. (Figure 4)

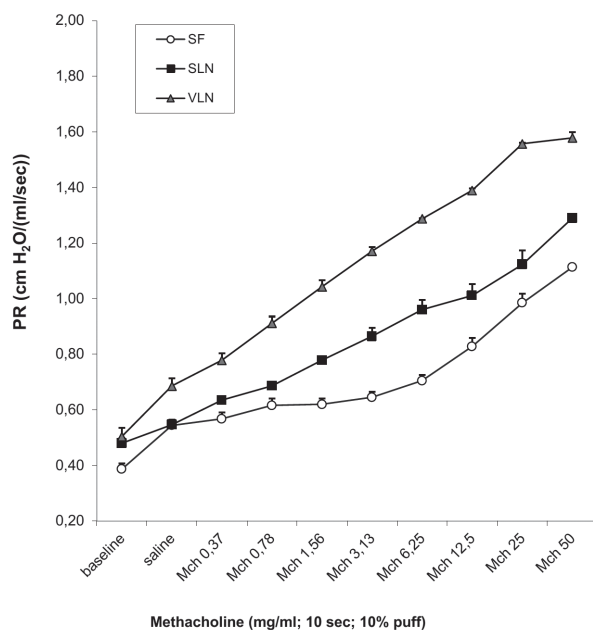
Furthermore, both the levels of TNF- $\alpha$  ( $754 \pm 94$  (FS) vs.  $717 \pm 80$  (HFS);  $P=0.770$ ) and IL-6 ( $458 \pm 76$  (FS) vs.  $458 \pm 62$  (HFS);  $P=1.000$ ) in lung homogenates were not reduced after administration of high-fat nutrition. (Figure 5) Although the total number of polymorphonuclear cells in plasma ( $67 \pm 12$  (FS) vs.  $71 \pm 7$  (HFS);  $P=0.802$ ) were not affected by the high-fat nutrition, there was a trend towards a reduced number of mononuclear cells in the plasma ( $35.2 \pm 4$  (FS) vs.  $26.5 \pm 2$  (HFS);  $P=0.053$ ). (Figure 6) Two hours after LPS administration there was no significant difference in both the TNF- $\alpha$  ( $378 \pm 85$  (FS) vs.  $275 \pm 79$  (HFS);  $P=0.397$ ) and IL-6 ( $157 \pm 44$  (FS) vs.  $198 \pm 48$  (HFS);  $P=0.161$ ) in the plasma. Also after animals were sacrificed plasma levels of TNF- $\alpha$  ( $211 \pm 63$  (FS) vs.  $224 \pm 70$  (HFS);  $P=0.900$ ) and IL-6 ( $157 \pm 44$  (FS) vs.  $198 \pm 48$  (HFS);  $P=0.535$ ) did not statistically significant differ





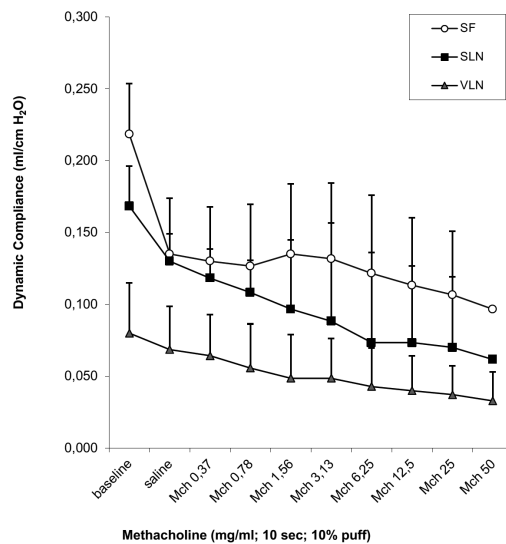
**Figure 2. Lung Injury Score.** Bar charts of the differences in lung injury score. The HFS ( $P=0.004$ ) had a significantly lower Lung Injury Score than the FS group. There were no significant differences between the HFS and HFV groups.

**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy.



**Figure 3a. Pulmonary resistance.** Preoperative administration of high-fat enteral nutrition did not reduce pulmonary resistance (FS vs HFS;  $P=0.757$ ). The pulmonary resistance was increased after abdominal vagotomy (HFS vs. HFV;  $P<0.001$ ).

**Abbreviations:** PR = Pulmonary Resistance, FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy.



**Figure 3b. Dynamic compliance.** Preoperative administration of high-fat enteral nutrition did not reduce pulmonary resistance (FS vs HFS;  $P=0.270$ ). The dynamic compliance was decreased after abdominal vagotomy (HFS vs. HFV;  $P<0.001$ ).

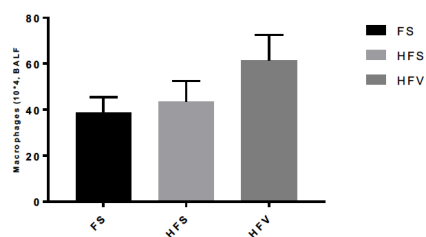
**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy.

### Vagotomy attenuates pulmonary function after administration of high-fat enteral nutrition

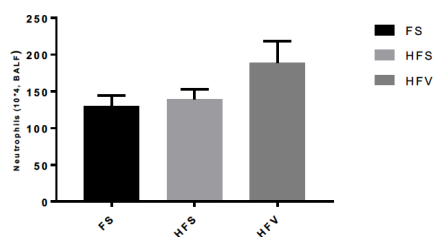
After administration of high-fat enteral nutrition, an abdominal vagotomy increased the pulmonary resistance ( $0.663 \pm 0.092$  cm H<sub>2</sub>O/(ml/sec) (HFS) vs.  $0.911 \pm 0.084$  H<sub>2</sub>O/(ml/sec) (HFV);  $P=0.040$ ) and decreased the dynamic compliance  $0.178 \pm 0.037$  H<sub>2</sub>O/(ml/sec) (HFS) vs.  $0.080 \pm 0.012$  H<sub>2</sub>O/(ml/sec) (HFV);  $P<0.001$ ). (Figure 3) The LIS was similar for both groups ( $0.307 \pm 0.053$  (HFS) vs.  $0.275 \pm 0.028$  (HFV);  $P=0.613$ ). (Figure 2) Both the number of macrophages ( $44 \pm 9$  (HFS) vs.  $61 \pm 11$  (HFV);  $P=0.328$ ) and the number of neutrophils ( $139 \pm 13$  (HFS) vs.  $189 \pm 29$  (HFV);  $P=0.279$ ) in BALF were not statistically significant elevated after abdominal vagotomy. (Figure 4) The levels of TNF- $\alpha$  ( $717 \pm 80$  (HFS) vs.  $688 \pm 104$  (HFV);  $P=0.832$ ) and IL-6 ( $458 \pm 62$  (HFS) vs.  $407 \pm 85$  (HFV);  $P=0.397$ ) in lung homogenates were not statistically significant increased after vagotomy. (Figure 5) Both the number of mononuclear cells ( $26.5 \pm 2$  (HFS) vs.  $24.8 \pm 3$  (HFV);  $P=0.462$ ) and the number

of polymorphonuclear cells ( $71 \pm 7$  (HFS) vs.  $61 \pm 11$  (HFV);  $P=0.459$ ) were not affected by vagotomy. (Figure 6)

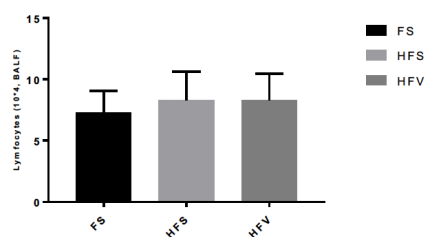
**A**



**B**



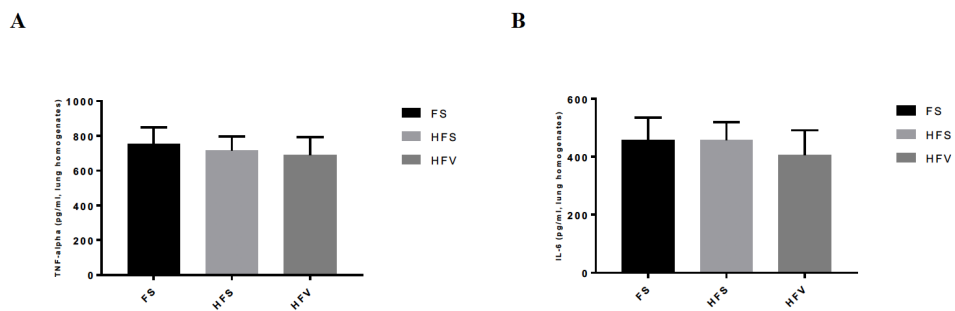
**C**



**Figure 4. Number of cells in BALF.** There were no statistical significant differences between groups in the number of (A) macrophages (B) neutrophils and (C) lymphocytes in the BALF.

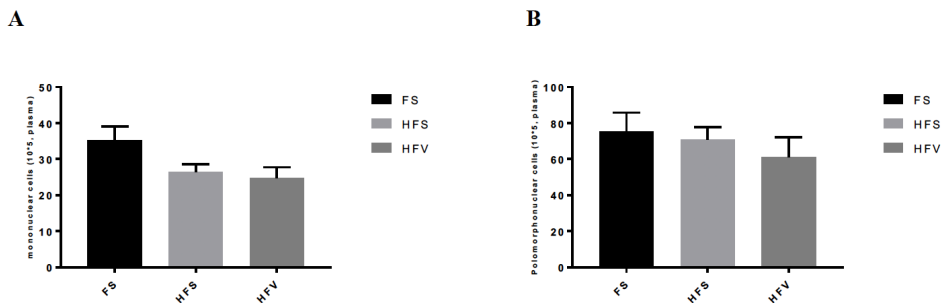
**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy. BALF: Bronchoalveolar lavage fluid.

Two hours after LPS administration TNF- $\alpha$  ( $275 \pm 79$  (HFS) vs.  $536 \pm 250$  (HFV);  $P=0.530$ ) and IL-6 ( $198 \pm 48$  (HFS) vs.  $221 \pm 61$  (HFV);  $P=0.573$ ) in plasma were not statistically significant increased after vagotomy. After termination there was no difference in the plasma level of TNF- $\alpha$  ( $224 \pm 70$  (HFS) vs.  $231 \pm 59$  (HFV);  $P=0.933$ ) and IL-6 ( $198 \pm 48$  (HFS) vs.  $221 \pm 61$  (HFV);  $P=0.774$ ) between groups. (Figure 7)



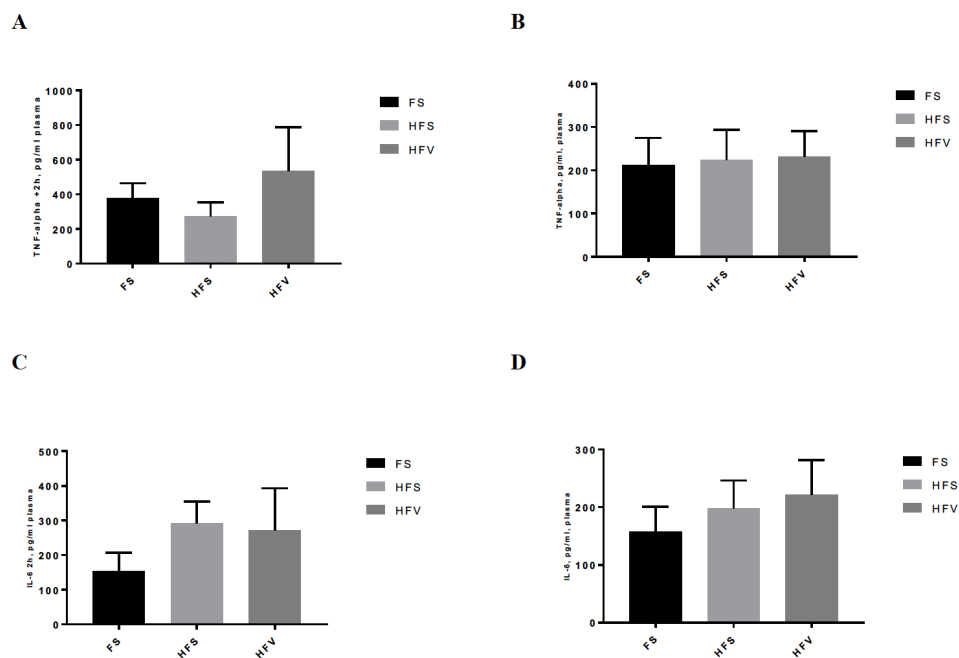
**Figure 5. TNF- $\alpha$  and IL-6 in lung homogenates.** No statistical significant differences between groups could be demonstrated in levels of TNF- $\alpha$  (A) or IL-6 (B) lung homogenates.

**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy. pg: picogram, ml: milliliter.



**Figure 6. Number of mononuclear cells in plasma and polymorphonuclear cells in plasma.** There was a trend towards a reduced number of (A) mononuclear cells in plasma ( $P=0.053$ ) after administration of high-fat enteral nutrition. An abdominal vagotomy did not influence the number of both mononuclear cells and (B) polymorphonuclear cells in plasma.

**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy



**Figure 7. TNF- $\alpha$  en IL-6 in plasma.** TNF- $\alpha$  and IL-6 in plasma did not statistically significant differ between groups both at 2 hours after administration of LPS (**A & C**) and after animals were sacrificed (**B & D**).

**Abbreviations:** FS: Fasting Sham, HFS: High-Fat Sham, HFV: High-Fat Vagotomy, pg: picogram, ml: milliliter, LPS: lipopolysaccharide.

## Discussion

The treatment of dysregulated pulmonary inflammation in patients after esophagectomy for cancer remains a critical issue. Therefore, new strategies to reduce the severity of pulmonary inflammation are needed. In the present study it is demonstrated that enteral administration of high-fat nutrition reduces LPS-induced histopathological lung injury. This effect remained, also after transection of the vagus nerve. Nevertheless, an abdominal vagotomy attenuated pulmonary function.

Previously published studies demonstrated that high-fat enteral nutrition was able to decrease both systemic and local inflammation via the vagus nerve in an experimental setting of hemorrhagic and endotoxic shock.<sup>13,15,17,18, 23</sup> High-fat enteral nutrition has several protective functions. At the moment high-fat nutrition enters the gastrointestinal tract, neuro-endocrine hormones are released. Cholecystokinin (CCK) is one of those hormones. After CCK is released, it activates the autonomic nerve system by binding to CCK-receptors on vagal afferents. Subsequently, vagal efferents will release acetylcholine, which binds to  $\alpha 7$ -nicotine acetylcholine receptors on tissue resident macrophages, resulting in a reduced release of macrophage-produced pro-inflammatory cytokines, such as TNF- $\alpha$ .<sup>15</sup> TNF- $\alpha$ , together with endotoxin, impairs intestinal barrier function.<sup>24</sup> This accelerates translocation of endotoxin during sepsis, causing a vicious cycle of ongoing endotoxin translocation. Moreover, high-fat nutrition increases plasma levels of chylomicrons and very low density lipoproteins (VLDL). The uptake of endotoxin by chylomicrons and VLDL reduces the bioactivity of endotoxin and the chylomicrons-induced increased hepatocellular uptake enhances clearance of circulating endotoxin.<sup>25-27</sup>

In the current study histopathological lung injury was significantly reduced after administration of high-fat nutrition, independently from the surgical procedure (sham or vagotomy). Furthermore, a clear trend towards an increased number of macrophages and neutrophils in the BALF and a reduced number of mononuclear cells in the plasma was demonstrated after abdominal vagotomy. This effect may be explained by a process called 'homing', in which leukocytes travel to, and accumulate at inflammatory sites.<sup>28,29</sup> This leads to an increased number of tissue-resident leukocytes and a reduced number of leukocytes in the plasma. This is an ongoing process, making the exact numbers of leukocytes (in BALF and plasma)

and differences between groups strongly dependent on time of measurement. In the current study, an abdominal vagotomy increased leukocyte influx into the lungs without increasing histopathological lung injury. This means that the pulmonary leukocytosis caused less tissue injury than expected. Hence, they may have been partially deactivated by the high-fat nutrition, as demonstrated by an absence of increased pulmonary TNF- $\alpha$  and IL-6 concentrations after abdominal vagotomy. However, the decreased pulmonary function after abdominal vagotomy shows that the nutritional intervention did not completely neutralize the pro-inflammatory effects of all tissue-resident leukocytes. Although transection of the abdominal vagus nerve might have inhibited direct activation of the autonomic nervous system, circulating CCK may still have activated the autonomic nervous system through a humoral route.<sup>30,31</sup> Furthermore, the endotoxin inhibiting effects of the high-fat nutrition induced presence of chylomicrons and VLDL are still present after vagotomy.

Although the current study demonstrated a clear advantage of preoperative high-fat enteral nutrition over fasting, and the clinical relevance is evident, the exact downstream mechanism underlying the observed effects remain to be investigated.

Implementation of enhanced recovery after surgery (ERAS) programs for esophagectomy have already demonstrated to improve postoperative outcomes.<sup>32</sup> These programs focus on early postoperative mobilization, different forms of anesthesia and nutrition. The results presented in this study demonstrate that preoperative administration of high-fat enteral nutrition reduces acute lung injury, also in the presence of an abdominal vagotomy. This implies a possible role for preoperative administration of high-fat enteral nutrition in patients undergoing esophagectomy for cancer. A preoperative dietary intervention may cause early autonomic nerve system activation, potentially reducing (the severity of) postoperative complications. A recently published randomized controlled trial, comparing perioperative high-fat enteral nutrition versus standard care in elective colorectal surgery, demonstrated no advantages of perioperative administration of high-fat nutrition in terms of postoperative pulmonary complications.<sup>33</sup> However, in this clinical trial patients received nutrition from 3 hours before until 6 hours after surgery, which increases the chance of developing postoperative aspira-

tion pneumonia. Furthermore, compared to colorectal surgery, the incidence of pulmonary complications after esophagectomy is much higher and its pathophysiology may be different. Therefore, a similar trial would be very valuable in patients undergoing esophagectomy.

Taken together, the current data show that preoperative administration of high-fat enteral nutrition reduces LPS-induced acute lung injury. These effects seem to be not only specific for the vagus nerve or are already present before vagotomy. This makes a preoperative dietary intervention translational to the clinic, potentially offering a therapeutic window to prepare patients for esophagectomy and potentially reduce the severity of postoperative encountered pulmonary complications.

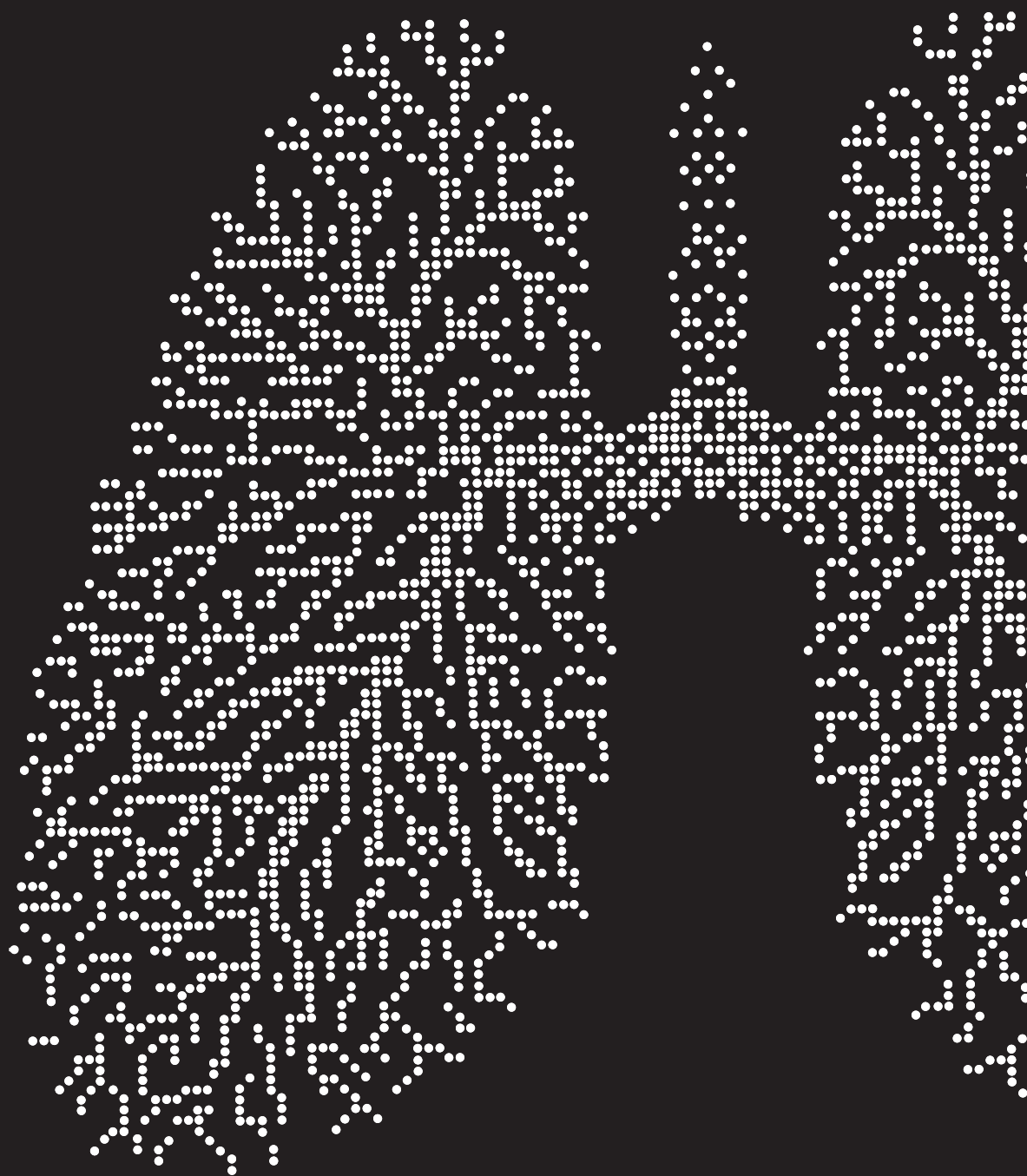


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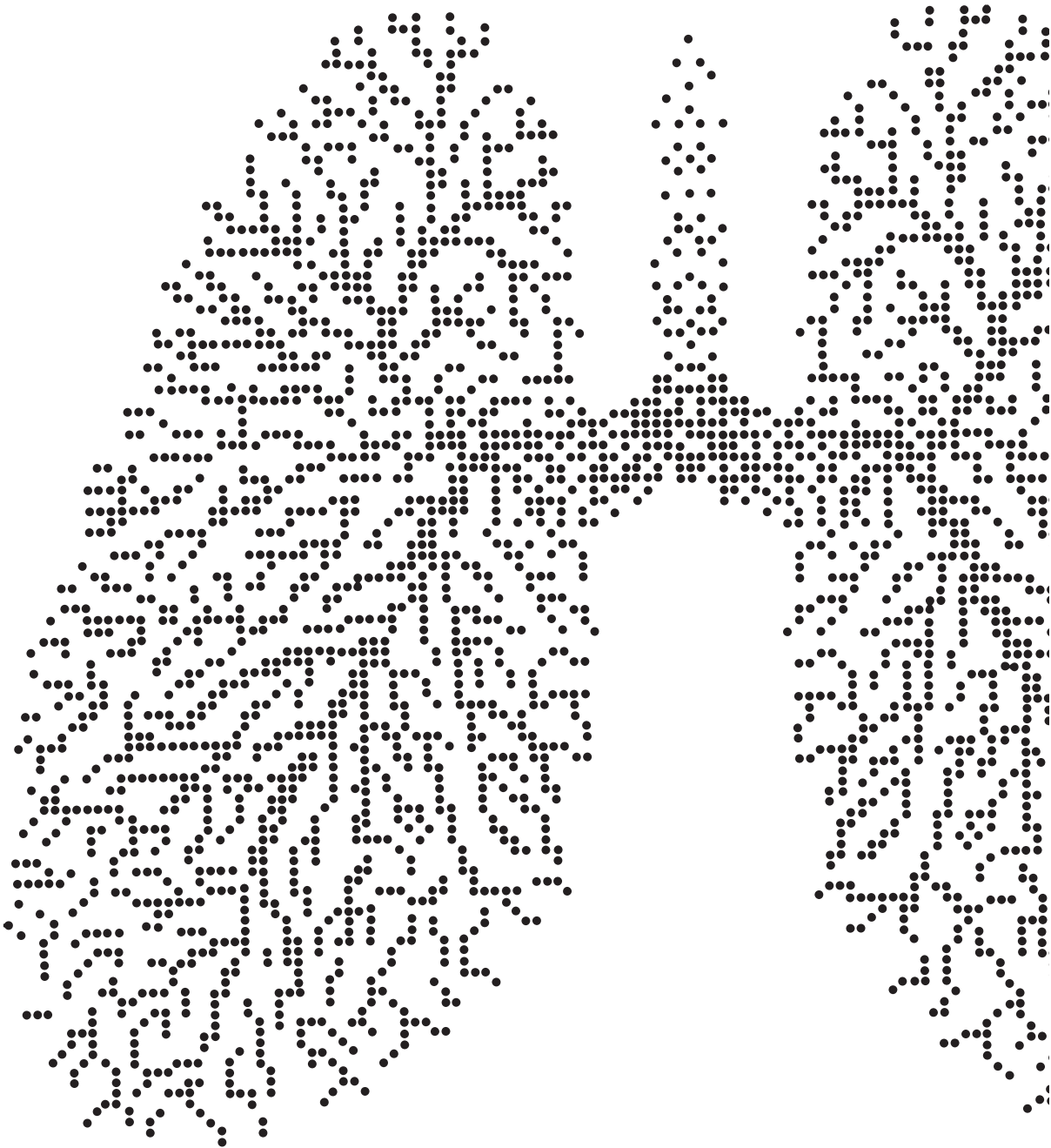
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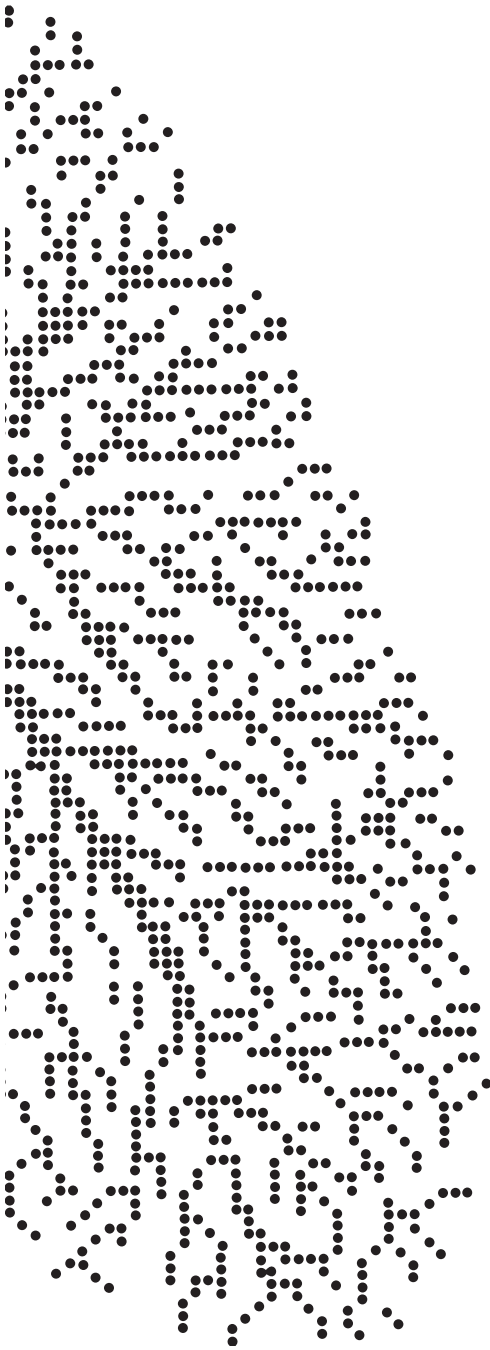
# PART IV

## SUMMARY AND GENERAL DISCUSSION



# Chapter 13

## Summary



Esophageal cancer has a fast growing incidence and is now the sixth leading cause of cancer-related mortality worldwide. The cornerstone of curative care is neoadjuvant chemoradiotherapy followed by esophagectomy. Nevertheless, esophagectomy is frequently followed by postoperative pulmonary complications. The work presented in this thesis concerns multiple strategies to reduce pulmonary complications after esophagectomy and to improve postoperative outcomes.



## **Part I “Minimally invasive surgery”**

The influence of minimally invasive techniques in general surgery has increased over the last decades. In 1992 the first minimally invasive esophagectomy was performed by Dr. Cuschieri. However, only in 2012 the first randomized controlled trial comparing open and minimally invasive esophagectomy was published. This trial demonstrated a reduced number of pulmonary infections, a shorter hospital stay and an improved short-term quality of life in patients in the minimally invasive group. **Chapter 2** describes the worldwide trends in surgical techniques for esophageal cancer surgery from 2007 to 2014. The preferred curative surgical treatment for esophageal cancer is a minimally invasive transthoracic esophagectomy with a two-field lymph node dissection and gastric conduit reconstruction. A strong worldwide trend towards minimally invasive surgery is observed. In 2007 the majority of patients underwent a classic, open esophageal resection with an anastomosis in the neck, whereas in 2014 almost half of the patients underwent a minimally invasive esophagectomy with an anastomosis in the thorax.

The work presented in **chapter 3** shows that the worldwide shift from open to minimally invasive esophageal surgery is also strongly present in the Netherlands. Whereas in 2011 only 2 out of 5 patients underwent a minimally invasive esophagectomy, in 2015 4 out of 5 patients underwent a minimally invasive esophagectomy. Although currently published studies demonstrate several advantages of minimally invasive esophagectomy, in this Dutch national study it appears that minimally invasive esophagectomy did not decrease the number of pulmonary complications. Moreover, it increased the anastomotic leakage- and reintervention rates. Nonetheless, it did reduce hospital stay and increased the lymph node yield. The increased number of complications after minimally invasive esophagectomy during this period may be explained by the long learning curve of this procedure. The rapid national spread of this surgical technique may have increased the number of postoperative complications.

The robot-assisted minimally invasive esophagectomy in the UMC Utrecht and its possible advantages over conventional minimally invasive techniques are presented in **chapter 4**. For example, the robot has instruments with an intracorporeal joint, a three-dimensional image with a high resolution and enlarged view. These properties may facilitate an extensive lymph node dissection and resection of large tumors.

**Chapter 5** demonstrates that there are no differences in the number of postoperative complications and short-term oncological outcomes between minimally invasive esophagectomy performed with the patient in the prone position versus the patient lying on the semiprone location. Both positions are safe and therefore it is recommended to position the patient according to the surgeons preference.

## **Part II “perioperative care”**

In this part of the thesis perioperative strategies to reduce pulmonary complications after esophagectomy are presented. Several pre-and postoperative interventions to reduce (the severity of) postoperative pulmonary complications are demonstrated.

It is essential to prepare patients for trimodality treatment in order to improve outcomes. Optimizing the nutritional status of the patient is a crucial part of this. One in three patients with esophageal cancer suffers from serious weight loss at diagnosis. Improvement of nutritional status can be achieved by means of direct oral feeding, or by nasojejunal, nasoduodenal tube, or jejunostomy feeding tube placement. Since oral nutrition is not always possible and nasojejunal and nasoduodenal tubes are uncomfortable and often dislocate, a jejunostomy feeding tube is a common option. **Chapter 6** demonstrates that early jejunostomy feeding tube placement causes few complications, improves the nutritional status of the patient, and leads to a high percentage of patients completing treatment with relatively few complications.

The aim of the research presented in **chapter 7** was to describe both the short and the long term consequences of a recurrent laryngeal nerve injury, in addition to the incidence and treatment of such an injury. The incidence of recurrent laryngeal nerve injury depends on the type of operation and is particularly prevalent in patients who underwent a transthoracic esophagectomy with a cervical anastomosis. This complication causes hoarseness and, due to a reduced swallowing function, an increased risk of postoperative pulmonary complications and a prolonged hospital stay. Half of the patients with a vocal cord injury did not have any remaining symptoms after 6 months. Approximately a quarter of the patients experienced a partial recovery of the vocal cord function and in a quarter of the patients there was no recovery after 6 months. As a result of this they had vocal cord surgery leading to full or partial recovery in 80% of patients.

Atrial fibrillation, a fast and irregular heart rhythm in both atria, is a frequently observed complication after esophagectomy. The pathophysiology of this complication remains unclear. It may be a result of direct damage to the pericardium during the operation, but also a lack of oxygen in the heart cells could lead to atrial fibrillation. This lack of oxygen can be caused by an infection. **Chapter 8** of this thesis shows that new-onset atrial fibrillation after esophagectomy is seldomly (9%) the only encountered postoperative complication and is strongly

associated with infectious complications, in particular anastomotic leakage and pulmonary complications. Furthermore, atrial fibrillation often occurs simultaneously with pulmonary complications, but it is usually diagnosed 4 days before the diagnosis of anastomotic leakage. Therefore atrial fibrillation may function as an early warning sign for the occurrence of anastomotic leakage.

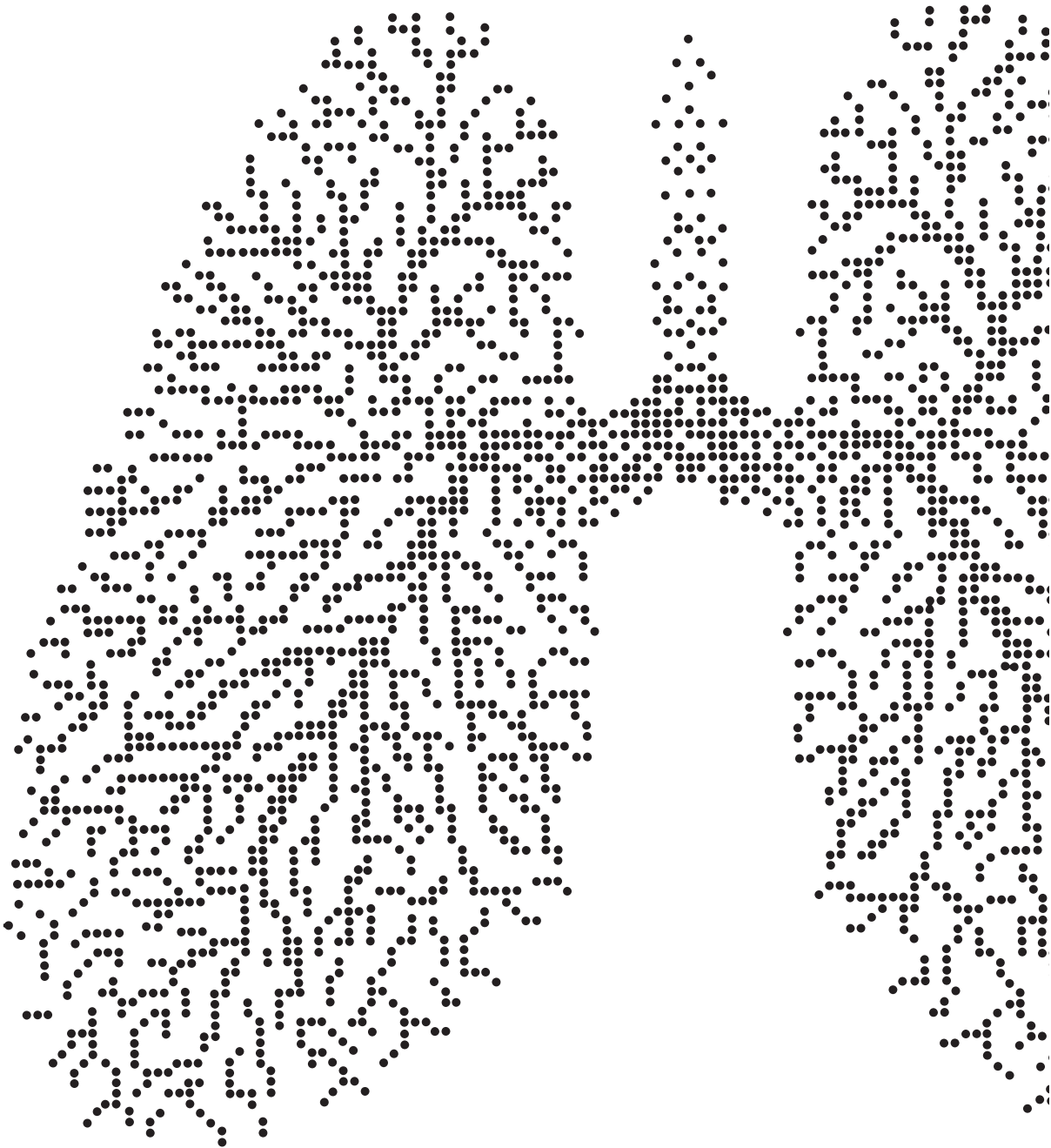
As described above, many patients suffer from pulmonary complications after esophagectomy for esophageal cancer. These complications, particularly pneumonia, increase both the stay at the intensive care unit and the surgical ward. Moreover, they increase postoperative mortality. Many studies have been conducted in order to reduce the number of pulmonary complications. However, interstudy and interhospital comparisons are hampered due to a lack of well-defined, validated definitions for pulmonary complications. In **chapter 9**, a scoring system to define pneumonia after esophagectomy was simplified and validated within the Netherlands. This scoring system, the Uniform Pneumonia Score, demonstrated to be a good definition for pneumonia after esophagectomy within the Netherlands. In **chapter 10** the Uniform Pneumonia score was validated in Virginia Mason Medical Center, Seattle, Washington. This study shows that the Uniform Pneumonia Score can serve as a means to define post-esophagectomy pneumonia. Utilization of this definition for pneumonia will improve both interstudy comparability and evaluation of new therapeutic strategies to reduce the incidence of pneumonia.

## **Part III “Neuroimmunity”**

Previous research has shown that the pulmonary branches of the vagus nerve can be spared during minimally invasive esophagectomy. This nerve potentially has an anti-inflammatory effect. The aim of the studies presented in this part of the thesis was to describe the effect of the vagus nerve on lipopolysaccharide (LPS) (a cell wall component of gram-negative bacteria which causes a strong immune response) induced acute lung injury in an experimental setting. Furthermore, we have investigated whether lipid-enriched nutrition can stimulate the vagus nerve.

In **chapter 11** it is demonstrated that a cervical vagotomy nerve increases LPS-induced acute lung injury and reduces pulmonary function in rats, whereas an abdominal vagotomy (sparing the pulmonary branches of the vagus nerve) does not significantly affect acute lung injury. These findings imply that the pulmonary branches of the vagus nerve may reduce acute lung injury and that sparing of these branches during esophagectomy may reduce pulmonary complications. However, this warrants further research in humans.

The experiments presented in **chapter 12** show that preoperatively administered lipid-enriched nutrition reduces LPS-induced acute lung injury in rats. These effects seem to be not only specific for the vagus nerve. This makes a preoperative dietary intervention translational to the clinic, potentially offering a therapeutic window to reduce the severity pulmonary complications after esophagectomy





# Chapter 14

General discussion

Future perspectives

Conclusions

## General discussion

### Reducing pulmonary complications after esophagectomy for cancer

In order to achieve cure, it is pivotal to optimize all parts of trimodality therapy for esophageal cancer patients. Since esophagectomy is a major, and very complex, surgical procedure, a certain degree of morbidity is inevitable. However, as physicians it is our task to reduce this to a minimum. This thesis demonstrated several intra- and perioperative clinical factors that may reduce postoperative morbidity.

### Minimally Invasive Surgery

The results of the international survey described in this thesis show that there has been a strong worldwide trend towards minimally invasive surgery.<sup>1</sup> Furthermore, the number of patients who underwent a McKeown esophagectomy has dropped, consequently leading to an increased number of patients who underwent an Ivor Lewis esophagectomy. The outcomes of the Dutch nationwide study presented in this thesis confirm these findings and demonstrate that minimally invasive esophagectomy has taken an enormous flight in the Netherlands.<sup>2</sup> These movements have presumably been the result of an increasing body of evidence suggesting that minimally invasive esophagectomy with an intrathoracic anastomosis improves postoperative outcomes.<sup>3-5</sup>

Although several studies demonstrated that minimally invasive esophagectomy leads to a reduced number of pulmonary infections, a shorter hospital stay and a better short-term quality of life compared to open surgery, several population based studies showed a significantly increased anastomotic leakage- and reintervention rate after minimally invasive esophagectomy.<sup>3,6-9</sup> Similar to the population based studies from the United Kingdom and the United States of America, the Dutch nationwide study revealed that the rapid introduction of minimally invasive esophagectomy has led to increased anastomotic leakage- and reintervention rates.<sup>2</sup> Nevertheless, it did reduce hospital stay and increased lymph node yield.

Recent literature demonstrated that minimally invasive esophagectomy has a substantial learning curve associated morbidity.<sup>10</sup> The length of the learning curve for anastomotic leakage is over 100 cases.<sup>11</sup> These outcomes warrant more dedicated proctor programs and additional research to investigate how learning associated morbidity may be further reduced and



preferably eliminated. The benefits of minimally invasive surgery will start to show after learning curve completion. Minimally invasive esophagectomy may be further optimized by using robotic assistance.<sup>12-15</sup> Besides its ergonomic benefits, robotic assistance enables the surgeon to reach the upper mediastinum and thoracic aperture. This facilitates an extended lymphadenectomy and might therefore increase survival rates.

### **Perioperative care**

To minimize failure to rescue rates following postoperative complications, early identification and treatment is essential.<sup>16</sup> This limits the development of the systemic inflammatory response syndrome, consequently reducing the severity of encountered complications. Postoperative complications may have linked pathophysiology, and therefore can also function as an early warning sign. In accordance with current literature, this thesis demonstrated that atrial fibrillation is a frequently encountered complication after esophagectomy and is rarely seen in isolation.<sup>17-20</sup> Atrial fibrillation is frequently associated with pneumonia and anastomotic leakage. It is most often diagnosed at the same day of pneumonia diagnosis and generally 4 days before the diagnosis of anastomotic leakage. Therefore, it may be of predictive value and initiation of an additional diagnostic work-up with a low threshold is therefore advisable to reveal underlying pathology when atrial fibrillation occurs after esophagectomy. Also, recurrent laryngeal nerve injury and pulmonary complications have a linked pathophysiology.<sup>21-23</sup> Similar to the results of this thesis, it has been demonstrated that recurrent laryngeal nerve injury increases the chance of aspiration pneumonia and therefore requires extra attention. However, in addition to current literature, this thesis demonstrated that recurrent laryngeal nerve injury also has a relatively high impact on long-term outcomes. Up to a quarter of all patients who suffer from recurrent laryngeal nerve paralysis after esophagectomy require vocal cord surgery within a year after esophagectomy. This is an extra argument to make a serious effort to minimize recurrent laryngeal nerve injury during esophagectomy.

### **Outcome definitions**

Until 2015 there was no widely accepted system for documenting the occurrence of complications associated with esophagectomy.<sup>24</sup> As a result, over 3000 articles in which outcomes after esophagectomy for cancer were reported before this time, have used a wide variety of

definitions for the same complications.<sup>25</sup> This means that comparing results of studies reporting on ‘identical’ complications is often like comparing apples and oranges, consequently hampering the applicability of findings. Although the publication by Low et al., in which most frequently encountered postoperative complications were standardized, has been a major step in developing standardized and uniformly used definitions for complications after esophagectomy for cancer, it still does not cover all definitions. The work in the second part of this thesis filled the most important gap. The Uniform Pneumonia Score is the only objective and validated score defining pneumonia after esophagectomy in Europe and the United States.<sup>26</sup> Taking this into account, it remains questionable whether the Uniform Pneumonia Score will also function in an Asian population. Patients in Western society are usually older and have a different set of comorbidities, such as those associated with obesity.<sup>27</sup> Furthermore, squamous cell carcinoma is more frequent in Asia and patients more often present with early stage cancer due to active screening programs.<sup>28</sup> This affects decision making regarding neoadjuvant regimens which consequently affects the postoperative course.<sup>29</sup> Next to tumor- and patient related factors, the health care system and the clinical decision making in Asian society is different from western society. Therefore, it would be valuable to validate the Uniform Pneumonia Score in an Asian population, preferably by independent researchers. Nevertheless, the Uniform Pneumonia Score is the best available definition for pneumonia after esophagectomy published to date and therefore it is strongly recommended to use this definition in future research.

### **Neuroimmunity**

Earlier we have demonstrated the exact course of the pulmonary vagus nerve branches and how minimally invasive surgery enables sparing these branches during transthoracic esophagectomy.<sup>30,31</sup> In the third part of this thesis we showed that the pulmonary branches of the vagus nerve have a protective function in lipopolysaccharide (LPS)-induced acute lung injury in an experimental setting. This indicates that the vagus nerve is an important mediator in the development of acute lung injury and that sparing of pulmonary vagus nerve fibres during surgery may be a therapeutic procedure to reduce pulmonary complications after transthoracic esophagectomy.

Although the exact downstream pathway underlying the observed effects of vagotomy warrants further investigation, it seems to be a combined effect of various autonomic and anti-inflammatory functions of the vagus nerve. The experiments in which rats underwent a cervical vagotomy clearly demonstrated a strong autonomic effect of the pulmonary branches of the vagus nerve on pulmonary function, whereas the experiments in which rats were given high-fat enteral nutrition showed the involvement of a neural based anti-inflammatory pathway. The work presented in the third part of this thesis offers an indication to preserve the pulmonary vagus nerve branches during transthoracic esophagectomy when it does not compromise oncological principles. Furthermore, preoperative administration of high-fat enteral nutrition to stimulate the vagus nerve might reduce the chance of developing a potentially lethal inflammatory response after esophagectomy.

## Future perspectives

Several important aspects of perioperative care in esophageal cancer surgery are addressed in this dissertation. However, major steps still need to be taken. As already pointed out, the Uniform Pneumonia Score needs validation in an Asian population. If the Uniform Pneumonia Score turns out to be valuable in Asia as well and it will be used as a standard definition in research worldwide, it may reveal the true effectiveness of intra- and perioperative strategies to reduce pneumonia after esophagectomy. Furthermore, it would also be interesting to validate this definition in a surgical cohort of non-esophagectomy patients.

The next step for minimally invasive esophagectomy will be its further implementation and centralization. The outcomes of minimally invasive esophagectomy may be improved by centralization of esophageal cancer care.<sup>32</sup> One may compare surgery to sports: extended experience and practice will lead to better results. This applies not only to the surgeon, but to all health care professionals involved in the esophageal cancer care chain. In order to achieve safe implementation of minimally invasive esophagectomy it is pivotal to follow strict guidelines and proctor programs. At the same time, further improvement of minimally invasive esophagectomy may be achieved with robotic assistance. Although robotic assistance may improve outcomes for both the surgeon (ergonomics) and the patient, costs are currently high. Since the da Vinci surgical system earned Food and Drug Administration (FDA) approval in 2000, Intuitive has enjoyed a fairly large head start in the field of robot-assisted minimally invasive surgery. However, for some years now, the competition has been brewing and a redistribution of the market is currently ongoing. Since October 2017 also TransEnterix earned FDA approval for its Senhance surgical system. This device, in contrast to the da Vinci Surgical system, features haptic feedback, enabling the surgeon to ‘feel’ the tissue. Also Medtronic, Johnson & Johnson and Verb Surgical are looking to enter the market this year. These developments will stimulate market forces, decrease costs and facilitate further implementation and development of robotic surgery. In terms of future developments in robotic surgery one should think of augmented reality. Using this technique a virtual image, like a CT-scan or MRI, may overlap a real-life camera feed. Augmented reality allows you to still keep in touch with the real world, while at the same time adding an extra layer. For example, this enables the surgeon to visualize the location and extent of a tumor and his relationship with surrounding structures. Also the creation of a three-dimensional panorama out of the

stereoscopic camera is expected in new robotic surgical system to increase the vision field of the surgeon.

Every little part of the human body may interact of which the vagus nerve is a perfect example. The work presented in this thesis shows that leaving original anatomy intact improves outcomes. Minimally invasive surgery facilitates preservation of the pulmonary branches of the vagus nerve and high-fat enteral nutrition stimulates this nerve which in turn reduces LPS-induced acute lung injury. The exact physiology remains unknown. Controlled electric stimulation of the vagus nerve may offer new opportunities to identify the exact pathway of vagus nerve controlled acute lung injury in an experimental setting. Nevertheless, its protective function has been demonstrated. Preservation as well as perioperative (nutritional) stimulation of the pulmonary branches of the vagus nerve may improve the immunological status of patients and protect them against postoperative pulmonary complications. Therefore, randomized controlled studies have to be conducted to investigate the use of the preservation and stimulation of the pulmonary branches of the vagus nerve in a clinical setting.

## Conclusions

### **Part I. Minimally invasive surgery**

**Chapter 2** The preferred curative surgical treatment of esophageal cancer is a minimally invasive transthoracic esophagectomy with a two-field lymph node dissection and gastric conduit reconstruction. A strong worldwide trend towards minimally invasive surgery is observed.

**Chapter 3** Mortality and pulmonary complications are similar for minimally invasive esophagectomy and open esophagectomy on a population based level. Anastomotic leaks and reinterventions are more frequently observed after minimally invasive esophagectomy.

**Chapter 4** The use of robot-assisted minimally invasive esophagectomy broadens indications for curative surgery.

**Chapter 5** The use of semiprone positioning in minimally invasive esophagectomy is safe, feasible and at least comparable to MIE in prone position in terms of oncological clearance and postoperative complications.

### **Part II. Perioperative Care**

**Chapter 6** Jejunostomy feeding tube placement can support nutrition to facilitate completion of trimodality therapy for esophageal cancer and jejunostomy feeding tube related complications are typically minor.

**Chapter 7** Recurrent laryngeal nerve injury after McKeown esophagectomy is associated with an increased pulmonary complication rate, longer hospital stay, and a moderate long-term recovery

**Chapter 8** New-onset atrial fibrillation after esophagectomy is highly associated with infectious complications and may serve as an early clinical warning sign for anastomotic leakage.

**Chapter 9** The Uniform Pneumonia Score has the potential to function as a standardized and uniformly used definition for pneumonia after esophagectomy in esophageal cancer research.

**Chapter 10** The Uniform Pneumonia Score confirms to be a valuable and easy implementable scoring system in a high-volume center in the United States of America.

### **Part III Neuroimmunity**

**Chapter 11** Preservation of the pulmonary branches of the vagus nerve may decrease LPS-induced acute lung injury. Vagotomy may therefore be an important factor in the occurrence of pulmonary complications following esophagectomy.

**Chapter 12** High-fat enteral nutrition decreases histopathological lung injury in LPS-induced acute lung injury. This indicates that preoperative administration of high-fat nutrition may reduce pulmonary complications after esophagectomy.

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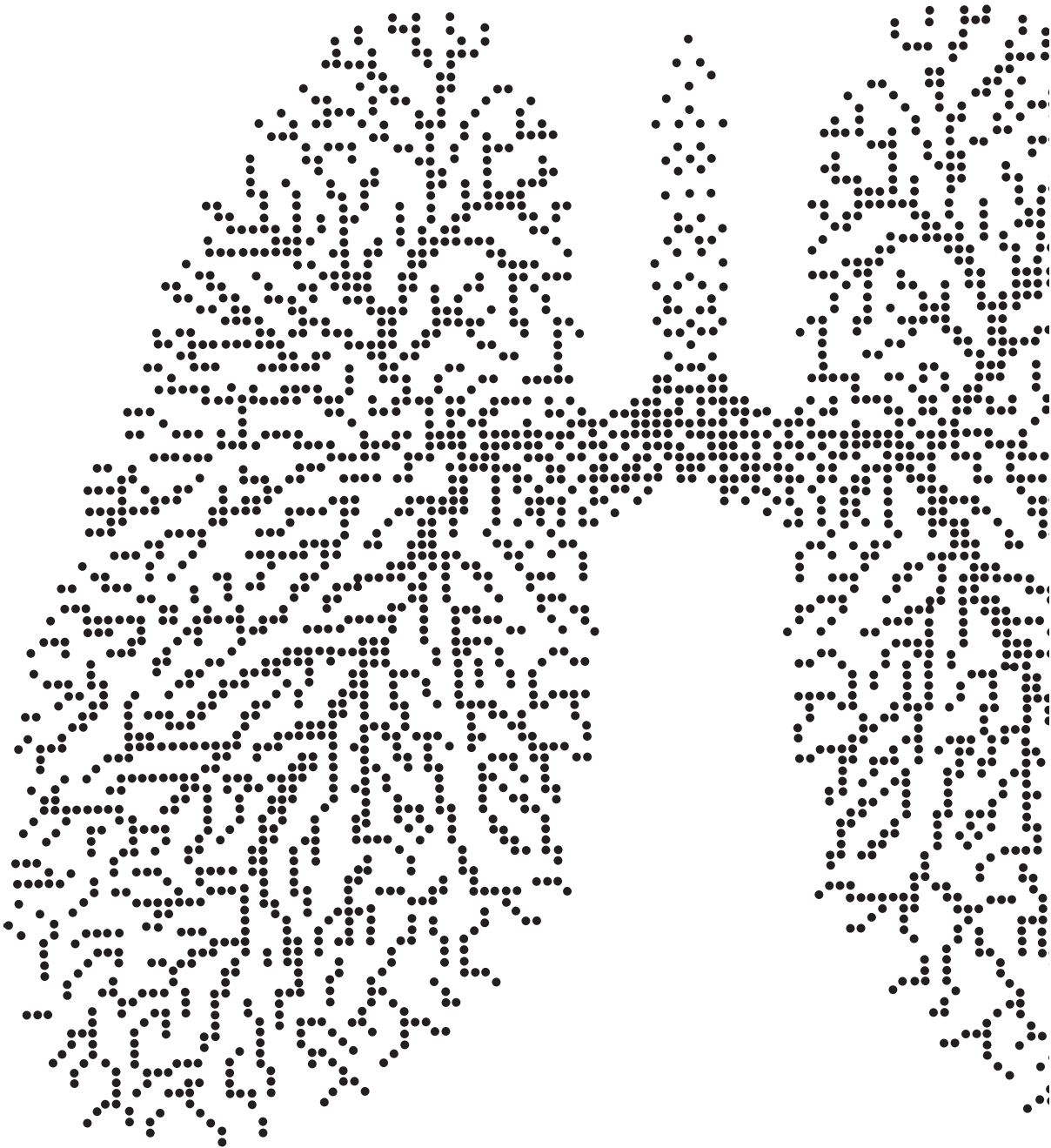
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# Chapter 15

Summary in Dutch

Letters to the editor

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Review committee

List of publications

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## Summary in Dutch

Slokdarmkanker treft jaarlijks meer dan 450.000 mensen wereldwijd, waarvan ongeveer 2000 mensen in Nederland. Het is een agressieve ziekte, mede gekenmerkt door zijn hoge mortaliteit (400.000 sterftegevallen per jaar). Een op de 4 patiënten komt op het moment van de diagnose nog in aanmerking voor een curatieve behandeling. De curatieve behandeling van het slokdarmcarcinoom bestaat uit neoadjuvante chemoradiotherapie gevolgt door een slokdarmresectie met een radicale lymfeklierdissectie en een buismaagreconstructie. Een slokdarmresectie wordt in meer dan de helft van de gevallen gevolgt door een of meerdere complicaties. Omdat de slokdarm een nauwe relatie heeft met de longen, worden pulmonale complicaties frequent gezien na de operatie. In dit proefschrift zijn meerdere strategieën onderzocht om het aantal en de ernst van pulmonale complicaties na slokdarmresectie te reduceren.

### Deel I “Minimaal invasieve chirurgie”

De invloed van minimaal invasieve technieken binnen de chirurgie is afgelopen decennia sterk toegenomen. In 1992 werd voor het eerst de minimaal invasieve slokdarmresectie beschreven door Cushieri. Echter, pas in 2012 werd het eerste gerandomiseerde onderzoek gepubliceerd waaruit duidelijk werd dat minimaal invasieve slokdarmchirurgie leidt tot minder pulmonale infecties, een kortere opnameduur en een betere kwaliteit van leven na de operatie. In **hoofdstuk 2** wordt beschreven wat de ontwikkelingen in de klinische praktijk zijn tussen 2007 en 2014. Door middel van een uitgebreide vragenlijst zijn wereldwijd, zowel in 2007 als in 2014, slokdarmchirurgen gevraagd naar hun behandelstrategieën. Hieruit blijkt dat er wereldwijd een verschuiving in het chirurgische behandelplan heeft plaats gevonden. Alwaar in 2007 de meerderheid van alle patiënten een klassieke, open slokdarmresectie onderging met een anastomose in de nek, werd in 2014 bijna de helft middels een minimaal invasieve operatie met een anastomose in de thorax behandeld. Deze studie laat zien dat er een sterke trend richting minimaal invasieve chirurgie in de behandeling van het slokdarmcarcinoom gaande is.

Uit het onderzoek gepresenteerd in **hoofdstuk 3** blijkt dat de wereldwijde verschuiving van open naar minimaal invasieve slokdarmchirurgie ook in Nederland sterk aanwezig is. Waar in 2011 nog 2 op de 5 patiënten een minimaal invasieve operatie ondergingen waren dat er

in 2015 4 op de 5. Al zijn in eerder gepubliceerd onderzoek veel voordelen beschreven van een minimaal invasieve benadering, in deze landelijke studie blijkt dat de minimaal invasieve slokdarmresectie niet heeft geleid tot een afname van pulmonale complicaties, maar wel tot een toename van naadlekkage en reïnterventies na de operatie. Desalniettemin verbleven patienten minder lang in het ziekenhuis na een minimaal invasieve operatie en werden er ook meer lymfeklieren geresecteerd. Het toegenomen aantal complicaties in de groep patienten die in deze periode een minimaal invasieve slokdarmresectie ondergingen is mogelijk te verklaren door de lange leercurve van deze procedure. Mogelijk heeft de snelle nationale verspreiding van deze operatieve techniek geleid tot meer complicaties.

**Hoofdstuk 4** beschrijft de robot geassisteerde slokdarmresectie in het UMC Utrecht en is een uiteenzetting van mogelijke voordelen die de robot levert ten opzichte van conventionele minimaal invasieve technieken. Zo faciliteert de robot een uitgebreide lymfeklierdissectie van grote tumoren middels instrumenten met een intracorporeel gewricht, een natuurgetrouw driedimensionaal beeld met een hoge resolutie en uitvergroete weergave. Deze eigenschappen van de robot bieden eventueel ook mogelijkheden in de behandeling van grote of moeilijk gelegen tumoren.

In **hoofdstuk 5** wordt beschreven dat er geen verschillen zijn in het aantal postoperatieve complicaties en oncologische uitkomsten tussen de minimaal invasieve operatie uitgevoerd met de patient in buikligging (prone) versus de patient die op de linker zijde (semiprone) ligt. Beide posities zijn veilig en daarom wordt aanbevolen om de positie te gebruiken waarbij de chirurg zich het meest comfortabel voelt.

## **Deel II “Perioperatieve zorg”**

Dit deel van het proefschrift beschrijft verschillende perioperatieve strategieën om het aantal, of de ernst van, pulmonale complicaties te reduceren.

Het is essentieel om de patient optimaal voor te bereiden op de behandeling om zodoende de uitkomsten te verbeteren. Een onderdeel van deze voorbereiding is het optimaliseren van de voedingsstatus van de patient. Een op de drie patienten met slokdarmkanker presenteert zich bij de huisarts met ernstig gewichtsverlies. Het verbeteren van de voedingsstatus kan worden gedaan middels een nasojejunale- of nasoduodenale sonde (sonde via neus in de dunne darm

of twaalfvingerige darm), orale voeding of het aanbrengen van een voedingsjejunostomie (voedingssonde via de buikwand in de dunne darm). Omdat orale voeding niet bij alle patiënten mogelijk is en de nasojejunale en nasoduodenale sondes oncomfortabel zijn en vaak luxeren, is de voedingsjejunostomie een veelgebruikte optie. **Hoofdstuk 6** laat zien dat het vroegtijdig in de behandeling plaatsen van een voedingsjejunostomie weinig complicaties geeft, de voedingsstatus van de patient verbetert, en leidt tot een hoog percentage aan patiënten dat de volledige behandeling afmaakt met relatief weinig complicaties.

Het doel van het onderzoek in **hoofdstuk 7** was om, behalve de incidentie en behandeling van peroperatief ontstane schade aan de nervus laryngeus recurrens, de gevolgen van een dergelijk letsel voor de patient op zowel korte als lange termijn te beschrijven. De incidentie van nervus laryngeus recurrens letsel hangt af van het type operatie en komt met name voor bij patiënten die een transthoracale slokdarmresectie hebben ondergaan waarbij een anastomose in de hals is gemaakt. Deze complicatie zorgt voor heesheid en dankzij een verminderde slikfunctie voor een verhoogde kans op postoperatieve pulmonale complicaties en een verlengde opnameduur. Op lange termijn (>6 maanden) liet de helft van de patiënten met een letsel van de nervus laryngeus recurrens volledig herstel zien zonder operatieve ingreep aan de stembanden. Bij ongeveer een kwart van de patiënten trad een partieel herstel op van de stembandfunctie en bij een kwart van de patiënten trad er geen herstel op waardoor zij zijn geopereerd aan de stembanden. 80% van deze laatste groep liet een volledig of partieel herstel van de stembandfunctie zien na de operatie.

Atriumfibrilleren, een snel en onregelmatig hartritme in beide boezems van het hart, is een vaak geobserveerde complicatie na een slokdarmresectie. Hoe deze complicatie ontstaat is nog onduidelijk. Het zou een gevolg kunnen zijn van directe schade aan het pericardium (hartzakje) tijdens de operatie, maar ook een gebrek aan zuurstof in de hartcellen zou kunnen leiden tot atriumfibrilleren. Dit zuurstofgebrek kan ontstaan door een infectie. **Hoofdstuk 8** van dit proefschrift laat zien dat atriumfibrilleren, ontstaan na een slokdarmresectie, bijna nooit (9%) als enige complicatie optreedt en sterk geassocieerd is met andere infectieuze complicaties, met name naadlekkage en pulmonale complicaties. Verder wordt in de hoofdstuk beschreven dat atriumfibrilleren vaak tegelijkertijd met pulmonale complicaties



optreedt, maar dat de diagnose meestal 4 dagen vóór de diagnose van naadlekkage wordt gesteld. Dit betekent dat dat atriumfibrilleren eventueel kan functioneren als een vroege waarschuwing voor het ontstaan van naadlekkage zo dat er tijdig diagnostiek en behandeling kan worden ingezet.

De meest voorkomende pulmonale complicatie na een slokdarmresectie is een longontsteking (pneumonie). Het is bewezen dat het optreden van een pneumonie de opnameduur, op zowel de chirurgische afdeling als de intensive care, verlengt en de kans op postoperatieve sterfte vergroot. Deze feiten onderstrepen het belang van onderzoek naar strategieën om de kans op het optreden van deze complicatie te verkleinen. Echter, de uitvoering van dit onderzoek wordt gehinderd door de afwezigheid van een gevalideerde definitie voor pneumonie. Momenteel bestaan er in de literatuur meer dan 18 verschillende definities voor pneumonie na slokdarmresectie, dit bemoeilijkt het vergelijken van resultaten van verschillende studies en ziekenhuizen.

In **hoofdstuk 9** wordt een eerder ontwikkelde definitie voor pneumonie, gebaseerd op het aantal witte bloedcellen, de hoogte van lichaamstemperatuur en de bevindingen bij radiologisch onderzoek van de longen, vereenvoudigd en zowel intern als extern gevalideerd in Nederland. Hier wordt beschreven dat deze definitie, de “Uniform Pneumonia Score”, een accurate definitie is voor pneumonie na slokdarmresectie binnen Nederland.

In **hoofdstuk 10** wordt de Uniform Pneumonia Score gevalideerd in een cohort Noord-Amerikaanse patienten die een slokdarmresectie hebben ondergaan in Seattle, Washington. Ook hier blijkt de Uniform Pneumonia Score een goede definitie voor pneumonie na slokdarmresectie te zijn. Dit onderzoek ondersteunt en vergroot de toepasbaarheid van dit scoringsmodel. Hieruit volgt dan ook de aanbeveling om de Uniform Pneumonia Score te gebruiken in toekomstig onderzoek met pneumonie na slokdarmresectie als uitkomstparameter.

### **Deel III “Neuro immuniteit”**

In eerder onderzoek is aangetoond dat de pulmonale takken van de nervus vagus kunnen worden gespaard tijdens een minimaal invasieve slokdarmresectie. Deze zenuw zou een supres-

sief effect kunnen hebben op inflammatie. Het doel van de onderzoeken in dit deel van het proefschrift was om het effect van de nervus vagus op acuut ontstane longschade gedurende septische shock te beschrijven in een dierexperimentele setting. Verder is in dit deel van het proefschrift onderzocht of deze zenuw met vetverrijkte voeding kan worden gestimuleerd.

In **hoofdstuk 11** wordt aangetoond dat het doornemen van de nervus vagus in de hals leidt tot een verergering van longschade en een vermindering van longfunctie in ratten waar acute longschade is geïnduceerd door het toedienen van lipopolysaccharide (celwandbestanddelen van gram-negatieve bacteriën die een sterke immuunrespons veroorzaken) via de luchtpijp. Op het moment dat de nervus vagus net onder het middenrif wordt doorgenomen (zo worden de aftakkingen naar de long gespaard) geeft dit geen effect op longschade. Deze bevindingen samen impliceren dat de pulmonale takken van de nervus vagus longschade kunnen verminderen en dat het sparen van de pulmonale takken van de nervus vagus gedurende een slokdarmresectie eventueel pulmonale complicaties kan reduceren. Echter, dit moet nog worden onderzocht in de praktijk.

Uit het onderzoek gepresenteerd in **hoofdstuk 12** blijkt dat vetverrijkte voeding lipopolysaccharide geïnduceerde acute longschade in ratten vermindert, zonder volledige afhankelijkheid van de nervus vagus. Dit betekent dat het pre-operatief voeden van patienten met vetverrijkte voeding eventueel kan leiden tot het voorkomen van pulmonale complicaties na slokdarmresectie, maar ook hier geldt dat dit nog in mensen moet worden uitgezocht.

Concluderend is een slokdarmresectie een zeer ingrijpende operatie, gekenmerkt door relatief veel postperatieve complicaties. Met name pulmonale complicaties worden vaak geobserveerd. Alle facetten van de behandelingen dienen geoptimaliseerd te worden om zodoende een maximaal resultaat te behalen. Zo kan een voedingsjejunostomie voor en tijdens behandeling de fysieke status van de patient verbeteren en het tijdig postoperatief herkennen van complicaties, zoals nervus laryngeus recurrens letsel en atrium fibrilleren, leiden tot vroegtijdig ingrijpen en andere complicaties voorkomen. Verder kan minimaal invasieve chirurgie het postoperatieve herstel versnellen mits de leercurve geassocieerde morbiditeit wordt gecontroleerd. Bovendien biedt minimaal invasieve chirurgie de mogelijkheden om peroperatief de pulmonale takken van de nervus vagus te sparen, waardoor pulmonale complicaties

eventueel gereduceerd kunnen worden. Om dit aan te tonen is verder onderzoek nodig.

Behoudens het optimaliseren van perioperatieve proces is het van belang dat we dezelfde taal spreken, en dus de zelfde definities hanteren. Door uniforme definities voor complicaties te gebruiken kunnen resultaten van ziekenhuizen en studies adequaat met elkaar kunnen worden vergeleken en verbeteringen worden gemaakt. Zo laat dit proefschrift zien dat de Uniform Pneumonia Score een goede en betrouwbare definitie is voor pneumonie na slokdarmresectie en zou daarom wereldwijd als uniforme definitie moeten worden gebruikt.

## Letters to the editor

### **Comment on: A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands**

*Miguel A. Cuesta, MD, PhD Jennifer Straatman, MD, PhD Donald L. van der Peet, MD, PhD Department of Surgery, VU University Medical Center, Amsterdam, the Netherlands*

We would like to congratulate Dr Seesing and all the co-authors on their clinically relevant publication.<sup>1</sup> In their propensity score-matched analysis, they compared the outcome of patients as operated through open versus minimally invasive esophagectomy (MIE) through the transthoracic route as carried out in the Netherlands. The data are based on the Dutch register (DUCA), obligatory for all centers doing esophageal surgery since 2011. The DUCA register has evolved, and nowadays with its center-specific control system and verification system, has come to signify how a Register should be organized and implemented all over the world. However, while reading their publication, a few remarks and questions can be put forward. One of the conclusions of the authors is that pulmonary complications were similar for open and MIE. However, these postoperative pulmonary complications could not fully be specified because the Register does not discriminate between clinically proven pneumonia, pleural effusion leading to drainage, pleural empyema, acute respiratory distress syndrome, or reintubation. We wonder about the comparison made between this conclusion and the outcome of the primary outcome of the traditionalinvasive versusminimallyinvasive esophagectomy study trial in which a comparison was made between MIE and open esophagectomy (OE) in a randomized way.<sup>2</sup> In our view, comparison is not possible because in the traditional invasive versus minimally invasive esophagectomy study trial, the postoperative pulmonary infection served as first goal of the study (and not the pulmonary infection plus pulmonary embolism). Our trial established a statistically significant difference in favor of the MIE group. In addition, we would like to reflect on the changes produced in esophageal surgery during the period for this study in the Netherlands. In the Netherlands, between 2011 and 2015, important shifts occurred regarding organization of the esophageal cancer care, implementation of neoadjuvant therapy, and the surgical approach of the esophageal cancer. These shifts occurred in the period of time of the study in terms of centralization of esophageal surgery in dedicated centers; extensive implementation of the chemoradiotherapy as neoadjuvant therapy accord-

ing to the chemoradiotherapy for oesophageal cancer followed by surgery study scheme,<sup>3</sup> and the quick implementation of the total MIE from 43% to 84% in the same period of time. Moreover, in the surgical approach by MIE, a shift has happened involving an important increase in favor of the intrathoracic anastomosis according to Ivor Lewis MIE procedure, progressing from almost nil to near 50% of all transthoracic operated patients. The rationale for this is based on the increase in the past years of the distal and junctional adenocarcinomas (currently 85%), for which the Ivor Lewis procedure seemed an ideal surgical intervention. On the contrary, the reason for the increase of MIE in the Netherlands have been 2-fold: first of all, the aim of upper gastrointestinal surgeons to avoid a thoracotomy, increasing the quality of life of the patients without compromising the oncologic completeness of the resection; and secondly, the optimal training program of fellows and young Dutch surgeons in these practices of minimally invasive surgery. Regarding the incidence of anastomotic leakage and reinterventions, we have also some remarks. After matching both groups, the authors found statistical differences between the MIE and OE for anastomotic leakage (21.2% vs 15.5%), and for reintervention rate (28.2% vs 21.1%), being both, leakage and reinterventions, closed related factors. Nevertheless, it is interesting to observe that despite the higher incidence of leakages and reinterventions in the MIE group, postoperative mortality is similar to the OE group. Moreover, looking at the subgroup analysis, they found that the leakages after MIE McKeown procedure were not different than rates found in the Open McKeown procedure; whereas for the Ivor Lewis approach, the MIE was clearly statistically worse than in the open approach (21% vs 10%). Hence, we wonder how large the number of patients was who were intervened by Ivor Lewis OE in the period of time of the study to permit this comparison. Moreover, Straatman et al<sup>4</sup> found analyzing the multicenter Dutch data of Ivor Lewis MIE that the anastomotic leakage was around 15.2% in highly dedicated centers, with a 30-day mortality rate of 2.1%. It is probably the case that this quick implementation of the Ivor Lewis MIE has been accompanied with a high rate of anastomotic leakages and reinterventions with no increase of the postoperative mortality. Moreover, Ivor Lewis MIE has evolved, in the Dutch centers, so that since 2015, the intrathoracic anastomosis has been standardized in many centers, whereby the percentage of leakages and reintervention seems to have been importantly reduced. It is important to regard this propensity study of the Dutch Register between 2011 and 2015 as an analysis of surgical practices during period of time in which im-

portant changes in esophageal surgery in the Netherlands has come about. Questions arise as what to do with the outcome here published, particularly regarding the 3 possible measures: to stop the MIE program; to adopt some hybrid procedure as suggested in the discussion; or to adopt corrective measures and perfect the procedures to get the best and optimal outcome for the patients. Up to now, the last option has been chosen in the Netherlands. In conclusion, the paper by Dr Seesing and co-authors addresses a very relevant subject. This serves as an important step in establishing what the future of the MIE can be and how important it is to register and analyze the data produced by every surgical community. Accordingly, we would have liked to receive more information and feedback concerning the addressed remarks.

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**Response: “A Propensity Score–matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands”**

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We thank Cuesta et al for their comments on our study. The question is posed whether the outcomes of our population-based study from the Netherlands can be compared to the TIME trial, a Dutch randomized study that compares minimally invasive (MIE) with open (OE) transthoracic esophagectomy.<sup>1,2</sup> We agree that a limitation of our study is that we used pulmonary complications as a composed primary outcome measure. There may have been a lower rate of pneumonia in patients in the minimally invasive group but this is then associated with more other pulmonary events including pleural effusion, empyema and adult respiratory distress syndrome or acute respiratory failure. We feel that the definition of pneumonia after esophagectomy is still ill defined as this was also one of the criticisms of the TIME trial. Secondly, differentiation of pneumonia from other pulmonary complications such as lobar atelectasis, effusion, and aspiration is not easy. Hence, for clinical practice, the number of pulmonary complications including other relevant outcomes is important, valid, and better reflects the burden of adverse events after esophagectomy. Starting from January 2016, the Dutch Upper Gastrointestinal Cancer Audit (DUCA) registers the specific pulmonary complications according to well defined criteria as recently published by Low et al.<sup>3</sup> in the *Annals of Surgery*. These outcomes will be available for future research. The authors also raise concerns about the comparison between OE and MIE for patients who underwent an Ivor Lewis approach. After propensity score matching (baseline table for this subgroup analysis was not included in the manuscript) 182 patients remained in both groups and we feel this number is sufficient to report some interesting observations in our article. We agree that the higher anastomotic leak rate for patients who underwent MIE possibly reflects a learning curve for the intrathoracic anastomosis. However, such a learning curve could not be studied as data from the DUCA are anonymized and already 42% of all esophagectomies in the Netherlands were performed by a minimally invasive approach at the start of data collection. Our finding is in line with a recent publication including almost 650 patients that underwent MIE.<sup>4</sup> This study

showed that there is a learning curve associated with the introduction of MIE and that more than 10% of patients experience learning curve–associated anastomotic leakage. This underlines the importance of establishing dedicated centers but even within high-volume hospitals, patients are at risk for side effects associated with changes in surgical techniques. Hence, insight into nationwide outcomes covering a period where MIE has taken an enormous flight is important, not only to stress the benefits but also to pay attention to possible harms of the procedure. Finally, the question is posed what to do with the results from this study. Should we stop MIE programs, adopt the hybrid procedure, or try to improve the current MIE procedure? Clearly, MIE is likely to be oncologically safe and even has some benefits over open esophagectomy.<sup>2,5,6</sup> However, these results were obtained in high-volume centers with operating surgeons who have passed their learning curve. Our study reports on an unselected group of patients and the data represent the daily practice and current outcomes. The data are externally valid and help the doctor and patient in decision making and show that OE is not inferior to MIE.

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**Seesing MFJ\***, Scheijmans JCG\*, Borggreve AS, van Hillegerbserg R, Ruurda JP. The predictive value of new-onset atrial fibrillation on postoperative morbidity after esophagectomy for cancer. *Diseases of the Esophagus* 2018

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## About the author

Maarten Frans Johan Seesing was born on Boxing Day (1987) in Wageningen. He is the son of Frans Seesing and Wilma Seesing - Tenten, and has two older siblings, Lonneke Seesing and Toine Seesing. Until the age of 18 he lived in Wageningen where he graduated secondary school at Scholengemeenschap Pantarijn. After graduation he moved to Utrecht to study medicine at the University of Utrecht.

During his study in Utrecht he enjoyed playing hockey (Phoenix) and rugby (USRS) and joined the fraternity Utrechtsch Studenten Corps. From the very first time Maarten entered an operation room he developed a special interest for surgery. Since he enjoys a bit of adventure besides study and work, he moved to Pretoria (South Africa) where he did an elective internship in traumatology at the department of general surgery and later on also at the department of orthopedic surgery in Sarajevo (Bosnia and Herzegovina).

During the last two years of medical school he grew specific interest in surgical oncology. After graduating medical school he got the opportunity to commence a PhD program at the department of Surgery in the UMC Utrecht focusing on pulmonary complications after esophagectomy for cancer. For that purpose he collaborated with many centers within the Netherlands and moved to Seattle for a research fellowship at Virginia Mason Medical Center. The results of his research are presented in this thesis. During his PhD program he also coordinated the LOGICA trial, a multicenter randomized controlled trial comparing open and laparoscopic surgery for gastric cancer. Being closely involved in both gastric and esophageal cancer surgery allowed him to explore upper gastrointestinal cancer surgery as a whole. Currently, Maarten still lives in Utrecht and is working as a resident not in training at the department of surgery of the Sint Antonius Hospital.

