SUMMARY
PART I  Assessment of current literature

The rising incidence of esophageal cancer is expected to continue in the near future. Optimization of management is therefore of great importance. Improved multimodality diagnostic tools for staging, neoadjuvant therapy and standardized surgical approach are the main fields of management. In Chapter 1 the possible causes for the increased incidence of esophageal cancer are discussed. This increase of incidence is related to the higher incidence of adenocarcinoma, whereas the incidence of squamous cell carcinoma has not changed significantly over the last years. Staging should include a gastroscopy with biopsy, endoscopic ultrasound for determining the “T” and “N” stage and computed tomography (CT) of neck, thorax and abdomen. The ultrasound of the neck could be more valuable in stead of the CT-scan of the neck. In addition, there is evidence that positron emission tomography (PET) could improve staging. Concurrent chemoradio- neoadjuvant therapy leads to a better survival after surgery. This is especially true for the patients with adenocarcinoma. Open esophagectomy is associated with a high morbidity, especially respiratory complications, and long in-hospital recovery. Minimally invasive surgery for esophageal cancer could lead to a lower incidence of respiratory complications, a shorter intensive care and hospital stay with preservation of the oncologic results. This is based on non-randomized studies. A systematic review and meta-analysis was performed in Chapter 2 of current comparative studies comparing minimally invasive esophagectomy with open esophagectomy. Ten studies met the inclusion criteria. The studies were categorized in three groups for the analysis: total minimally invasive vs. open transthoracic esophagectomy (group 1); thoracoscopy and laparotomy vs. total open transthoracic esophagectomy (group 2); laparoscopic vs. open transhiatal esophagectomy (group 3). An overall trend was observed in favor of the minimally invasive procedures for major morbidity, respiratory complications, anastomotic leakage, mortality, length of hospital stay and blood loss. In the meta-analysis no significant differences was observed, in group 2 a significant lower incidence of anastomotic leakage was seen in the thoracoscopy group. No meta-analysis could be performed in group 3. The results in this systematic review are based on case-control studies. Randomized trials are needed for assessing the role of minimally invasive esophagectomy.

Standardization of esophageal resection could improve outcome and facilitate better multicenter research. In the past the level of anastomosis, cervical or thoracic, has been investigated in order to designate the best location. Four randomized trials have been conducted. These trials are appraised, and where appropriate a meta-analysis is performed, in Chapter 3. All studies had a relative small sample size and were of moderate quality. In the meta-analysis for which three of the four trials were included, cervical anastomosis was associated with a higher risk of leakage and recurrent nerve injury. Because of the limited randomized evidence, future trials in current clinical settings with larger sample sizes are needed to provide sufficient evidence.
Since the evidence in favor of one location is not clear, both cervical and thoracic anastomosis is used for gastric tube reconstruction. In minimally invasive esophagectomy the cervical anastomosis is performed through a cervicotomy. In an Ivor-Lewis esophagectomy (involving a thoracic anastomosis) the minimally invasive technique can be performed with the use of several techniques. These techniques are discussed in Chapter 4. The most frequent used technique is the stapled one. This can be performed by introducing the anvil orally or through a mini-thoracotomy.

The abovementioned assessment involving minimally invasive esophagectomy exposed the shortcomings in literature and therefore current clinical practice. These include the unavailability of randomized trials comparing minimally invasive esophagectomy with open esophagectomy. Also, that designating the optimal level of anastomosis needs further research. Lastly, standardization of surgery is needed particularly in minimally invasive Ivor Lewis esophagectomy.

**PART II  Minimally invasive esophagectomy in retrospect**

Introduction of minimally invasive esophagectomy should be carried out by surgeons with extensive experience in minimally invasive surgery. The centers where this surgery is performed should have safety procedures and quality checks designed for it. Appraisal of the oncologic outcome should be emphasized in minimally invasive esophagectomy. Reviewing own single center experiences is one of the methods in ensuring a safe introduction and performance of minimally invasive procedures.

In this part, investigation of minimally invasive esophagectomy in the VU university medical center was centered. In Chapter 5 a retrospective analysis was conducted of laparoscopic transthiatal esophagectomy, these patients were compared with a historic cohort who underwent an open transhiatal esophagectomy. A total of 100 patients were included in the analysis. No significant differences in post-operative complications and oncologic outcome were observed between the groups. However, significant less blood loss, shorter intensive care unit and hospital stay was observed in the patients undergoing a laparoscopic transhiatal esophagectomy. Again randomized studies are needed to evaluate the outcome without possible bias, which could be present in retrospective analysis. Similarly, forty patients undergoing a minimally invasive transthoracic esophagectomy in prone position are analysed in Chapter 6. The oncologic outcome was consistent with open procedures reported in literature.

**PART III  Prospective minimally invasive esophagectomy**

In order to provide sufficient evidence regarding minimally invasive esophagectomy we conducted a multicenter, randomized trial: the TIME-trial. The protocol of this trial is reported in Chapter 7. Due to reviewer and editorial adjustments of the study, the definite article (Chapter 8) differs somewhat from the protocol. This first multicenter, randomized trial in the world was powered in the assumption that the incidence of respiratory complications (i.e. respiratory infections) would be significant lower in the minimally invasive group. Fifty-two patients in the open and 55 patients in the minimally invasive group were analyzed. A significant reduction in the incidence
of in-hospital respiratory infection of 25% was associated with the MIE. This also resulted in a significant shorter hospital stay (4 days). In addition, a significant better 6 weeks post-operative quality of life was observed in the MIE group. Importantly, the pathologic parameters were similar between the groups. We therefore conclude that minimally invasive esophagectomy in prone position for esophageal cancer is a safe procedure, resulting improved post-operative recovery compared to the open procedure. Minimally invasive esophageal resection in prone position procedure should be the preferred approach in patients with resectable esophageal cancer with a World Health Organization condition of ≤2.

In Chapter 9 the immunological response to open and minimally invasive esophagectomy was compared in this first randomized trial. The response was measured in a pilot of 27 patients. A significant higher white blood count, interleukin-8 and prolactin levels was observed in the open group after 1 week. Larger trials are however needed for further assessment of these results.

Minimally invasive Ivor Lewis esophagectomy has only been described in case reports in current literature. An analysis was performed in Chapter 10 of the patients in the VU university medical center who underwent an open or minimally invasive Ivor Lewis esophagectomy. A trend to better respiratory outcome was observed in the group who had a minimally invasive procedure.

A subgroup in the TIME-trial of the VU university medical center underwent an esophagectomy with a thoracic anastomosis. This group was compared with the cervical anastomosis group in Chapter 11 in order to assess anastomotic outcome. A significant higher incidence of recurrent nerve injury and more difficulties in talking in the short-term quality of life assessment was observed in patients who underwent esophagectomy with a cervical anastomosis. No significant differences with regard to other morbidity were observed in this sub analysis. These short-term outcomes should be taken into account when deciding the level of anastomosis for distal or GE junction tumors.

In Chapter 12 predictors of respiratory complications in the TIME-trial are investigated. In both a univariate and multivariate analysis a body mass index >25 and an open esophagectomy were significantly associated with respiratory infections. The positive impact of minimally invasive esophagectomy on respiratory infections is therefore substantial.