Improving the outcomes of esophagectomy: anatomic, surgical and postoperative aspects

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ABSTRACT

Esophagectomy is known for its high postoperative morbidity and mortality rates. In case of esophageal cancer, a transthoracic approach is often preferred since this allows for mediastinal lymphadenectomy, removing potential metastases. However this is frequently associated with pulmonary complications, increasing the need for intensive care unit treatment and mortality. Therefore this thesis aims to improve the outcome of esophagectomy.

A literature review shows that pulmonary complications are reduced by a minimally invasive approach and starting enteral nutrition early postoperatively. Preoperative optimization of patient performance, administration of anti-inflammatory medication perioperatively and prone-positioning are promising interventions, requiring further investigation. However, valid inter-study comparisons cannot be made since many different definitions are used for pneumonia. Therefore a recently proposed definition, the Utrecht Pneumonia Score (UPS) was revised and internally and externally validated, showing excellent discrimination and calibration. Currently this is the only validated definition for post-esophagectomy pneumonia available.

Inflammation may be the final common pathway in the multifactorial etiology of pulmonary complications following esophagectomy. Consequently several randomized studies investigated the effect of perioperative glucocorticoid administration, but sample sizes were too small. Therefore, we performed a meta-analysis, showing that weight dependent dose of methylprednisolone significantly reduces pulmonary complications, emphasizing the hypothesis that inflammation may be pivotal.

Another important regulatory pathway in inflammation and pulmonary function, affected by esophagectomy, runs via the vagus nerve. A vagotomy is performed as part of an esophagectomy due to its course next to the esophagus, but selective sparing of pulmonary branches may be feasible. Since the regional anatomy is complex we performed an anatomical and histological study, a study during thoracoscopic esophagectomies *in vivo,* a magnetic resonance imaging study *in vivo*. These show extensive pulmonary innervation, and indicate how these vagal branches can be spared. These also describe the meso-esophagus, a previously undescribed connective tissue layer. This courses from esophagus to aorta, dividing the posterior mediastinum in two compartments. Based on the anatomical mapping, feasibility of thoracoscopic pulmonary vagus nerve branches sparing esophagectomy was studied in human cadavers. This procedure is feasible, but attention should be given to removal of all peribronchial lymph nodes.

The vagus nerve can be activated through enteral nutrition leading to dampening of postoperative inflammation. However, a nil-by-mouth strategy following esophagectomy is standard of care in many centers. Through a systematic literature review and retrospective evaluation of routine jejunostomy tube feeding, we demonstrated the need to investigate early oral intake. However, concerns are increased severity of anastomotic leakage and (aspiration) pneumonia. Therefore we performed a single-arm, multicenter trial showing that early oral intake following minimally invasive esophagectomy is feasible and does not increase morbidity. Chyle leakage is an complication of enteral nutrition. Through a large retrospective analysis we have shown that the majority can be managed by dietary measures only.

In conclusion in this thesis a technique to spare the pulmonary branches of the vagus nerve during thoracoscopic esophagectomy is validated and the safety and feasibility of early start of oral intake following minimally invasive esophagectomy are shown. Further studies are needed to determine the effects of these interventions.

Keywords: Minimally invasive esophagectomy; Anatomy; Nutrition; Pneumonia; Inflammation; Vagus nerve; Chyle leakage; Meso-esophagus

CONTENT

ABSTRACTS

Chapter 2. Strategies to reduce pulmonary complications after esophagectomy

Esophagectomy, the surgical removal of all or part of the esophagus, is a surgical procedure that is associated with high morbidity and mortality. Pulmonary complications are an especially important postoperative problem. Therefore, many perioperative strategies to prevent pulmonary complications after esophagectomy have been investigated and introduced in daily clinical practice. Here, we review these strategies, including improvement of patient performance and technical advances such as minimally invasive surgery that have been implemented in recent years. Furthermore, interventions such as methylprednisolone, neutrophil elastase inhibitor and epidural analgesia, which have been shown to reduce pulmonary complications, are discussed. Benefits of the commonly applied routine nasogastric decompression, delay of oral intake and prophylactic mechanical ventilation are unclear, and many of these strategies are also evaluated here. Finally, we will discuss recent insights and new developments aimed to improve pulmonary outcomes after esophagectomy.

Chapter 3. In- and external validation of a multivariable model to define hospital-acquired pneumonia after esophagectomy

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 and proper validation of methods to prevent postoperative pneumonia. We aimed to simplify and validate an existing scoring model to define pneumonia following esophagectomy.
Patients and methods The Utrecht Pneumonia Score (UPS), 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). The internal and external model performance were evaluated in terms of discrimination and calibration.
Results In the revised Utrecht Pneumonia Score (rUPS), points are assigned based on: the temperature (≥36.1 and ≤38.4=0 points and ≤36.0°C or ≥38.5°C=1 point), the leucocyte count (≥4.0 and ≤11.0=0 points and <4.0 or >11.0=1 point) and the findings of pulmonary radiography (no infiltrate=0 points; diffuse infiltrate=1 point and well circumscribed infiltrate=2 points). Pneumonia is registered in case of ≥2 points, of which at least 1 point should be based on 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.
Conclusion The rUPS can serve as a means to define post-esophagectomy pneumonia. Utilization of a uniform definition for pneumonia will improve inter-study and inter-hospital comparability and improve the evaluations of new therapeutic strategies to reduce the pneumonia incidence.

Chapter 4. Perioperative methylprednisolone for transthoracic esophagectomy: A review and meta-analysis

Background Severe pulmonary complications occur frequently following transthoracic esophagectomy. An exaggerated immunological response is probably a main driving factor, and this might be prevented by perioperative administration of a glucocorticoid.
Objective To determine the clinical benefits and harms of perioperative glucocorticoid during transthoracic esophagectomy, using pulmonary complications as the primary outcome. Mortality, anastomotic leakage rate and infection were secondary outcomes.
Materials and methods A systematic review of interventional trials with a meta-analysis of randomized controlled trials (RCTs).
Results The search retrieved seven RCTs and four interventional nonrandomized studies. In total, 367 patients received perioperative glucocorticoid and 415 patients did not. A meta-analysis of the RCTs showed no significant effect of glucocorticoid. For pulmonary complications, the pooled risk ratio was 0.69 [95% confidence interval (CI) 0.26 to 1.79], for anastomotic leakage 0.61 (95% CI 0.23 to 1.61) and for infections 1.09 (95% CI 0.41 to 2.93). A subgroup analysis of RCTs that used weight-dependent dosing within 30min preoperatively showed a pooled risk ratio of 0.28 (95% CI 0.10 to 0.77) for pulmonary complications compared with placebo.
Conclusion In this meta-analysis, perioperative administration of glucocorticoid did not affect the risk of pulmonary complications after transthoracic esophagectomy, nor did it cause adverse effects. A subgroup analysis showed that a weight-dependent dose of methylprednisolone 10 to 30mgkg^{-1} within 30min preoperatively might be the most promising dosing regimen for further research.

Chapter 5. Topography and extent of pulmonary vagus nerve supply with respect to transthoracic esophagectomy

Pulmonary complications are frequently observed after transthoracic esophagectomy. These complications may be reduced by sparing the vagus nerve branches to the lung. However, current descriptions of the regional anatomy are insufficient. Therefore, we aimed to provide a highly detailed description of the course of the pulmonary vagus nerve branches. In 6 fixed adult human cadavers, bilateral microscopic dissection of the vagus nerve branches to the lungs was performed. The level of branching and the number, caliber and distribution of nerve branches were described. Nerve fibers were identified using neurofilament immunohistochemistry, and the nerve caliber was measured using computerized image analysis. Both lungs were supplied by a predominant posterior and a smaller anterior nerve plexus. The right lung was supplied by 13 (10-18) posterior and 3 (2-3) anterior branches containing 77% (62-100%) and 23% (0-38%) of the lung nerve supply, respectively. The left lung was supplied by 13 (8-13) posterior and 3 (2-4) anterior branches containing 74% (60-84%) and 26% (16-40%) of the left lung nerve supply, respectively. During transthoracic esophagectomy with *en bloc* lymphadenectomy and transection of the vagus nerves at the level of the azygos vein, 68-100% of the right lung nerve supply and 86-100% of the inferior left lung lobe nerve supply were severed. When vagotomy was performed distally to the last large pulmonary branch, 0-8% and 0-13% of the nerve branches to the right middle/inferior lobes and left inferior lobe, respectively, were lost. In conclusion, this study provides a detailed description of the extensive pulmonary nerve supply provided by the vagus nerves. During esophagectomy, extensive mediastinal lymphadenectomy denervates the lung to a great extent; however, this can be prevented by performing the vagotomy distal to the caudalmost large pulmonary branch. Further research is required to determine the feasibility of sparing the pulmonary vagus nerve branches without compromising the completeness of lymphadenectomy.

Chapter 6. A new concept of the anatomy of the thoracic esophagus: the meso-esophagus

Background During thoracoscopic esophageal surgery we observed not previously described fascia-like structures. Description of similar structures in rectal cancer surgery, was of paramount importance in improving the quality of resection. Therefore we aimed to describe a new comprehensive concept of the surgical anatomy of the thoracic esophagus with definition of the meso-esophagus.
Materials and methods We retrospectively evaluated 35 consecutive unedited videos of thoracoscopic esophageal resections for cancer, to determine the surgical anatomy of the esophageal fascia's, vessels and lymphatic drainage. The resulting concept was validated in a prospective study, including 20 patients at three different centers. Additional confirmation was sought by a histologic study of a cadaver's thorax.
Results A thin layer of connective tissue around the infra-carinal esophagus, involving the lymph nodes at the level of the carina, was observed during thoracoscopic esophagectomy in 32 of the 35 patients included in the retrospective study and in 19 of the 20 patients included in the prospective study. A thick fascia-like structure from the upper-thoracic aperture to the lower-thoracic aperture was visualized in all patients. This fascia is encountered between the descending aorta and left aspect of the infracarinal esophagus. Above the carina it expands on both sides of the esophagus to lateral mediastinal structures. This fascia contains esophageal vessels, lymph vessels and nodes and nerves. The histologic study confirmed these findings.
Conclusions Here we described the concept of the "meso-esophagus". Applying the description of the meso-esophagus will create a better understanding of the esophageal anatomy, leading to more adequate and reproducible surgery.

Chapter 7. Histology and magnetic resonance imaging confirmation of the meso-esophagus

Background Recently a layer of connective tissue, "the meso-esophagus" was discovered in the mediastinum. The relations with other peri-esophageal fascias have not been described, and it is unclear if the meso-esophagus can be visualized by non-invasive imaging. This study aimed to provide a comprehensive description of the peri-esophageal fascias and assessed if the meso-esophagus can be visualized by MRI.
Materials and methods MRI was performed on a human cadaver and followed by a histologic study of transverse tissue sections of the peri-esophageal tissue between the thyroid gland and the diaphragm. Subsequently a prospective study including patients with esophageal cancer was performed. Preoperative motion-triggered MRI scans were independently assessed for the presence and location of the meso-esophagus.
Results The meso-esophagus was visualized in the cadaver on MRI images, macroscopic tissue sections, after histologic staining and on MRI images obtained in vivo. The meso-esophagus courses from the ventral aspect of the descending aorta to the left lateral aspect of the esophagus. The meso-esophagus divides the posterior mediastinum in two distinct compartments: an anterior compartment containing the esophagus, (carinal) lymph nodes and vagus nerves, and a posterior compartment, containing the azygos vein, thoracic duct and lymph nodes. The meso-esophagus was observed in most (67-85%) MRI scans with moderate inter-observer agreement. The fascias above the aortic arch and at the level of the diaphragm were in line with the currently available anatomic descriptions of the fascias in the neck and of the phrenico-esophageal ligament.
Conclusions This study confirms the presence of the previously described meso-esophagus and provides a comprehensive, detailed description of the peri-esophageal fascias. For the first time the meso-esophagus has been visualized in vivo by MRI. Further studies are needed to determine the clinical implications.

Chapter 8. Preserving the pulmonary vagus nerve branches during thoracoscopic esophagectomy

Background Pulmonary vagus branches are transected as part of a transthoracic esophagectomy and lymphadenectomy for cancer. This may contribute to the development of postoperative pulmonary complications. Studies in which sparing of the pulmonary vagus nerve branches during thoracoscopic esophagectomy is investigated are lacking. Therefore this study aimed to determine the feasibility and pitfalls of sparing pulmonary vagus nerve branches during thoracoscopic esophagectomy.
Methods In 10 human cadavers a thoracoscopic esophagectomy was performed while sparing the pulmonary vagus nerve branches. The number of intact nerve branches, their distribution over the lung lobes and the number and location of the remaining lymph nodes in the relevant esophageal lymph node stations (7, 10R and 10L), were recorded during microscopic dissection.
Results A median of 9 (range 5-16) right pulmonary vagus nerve branches were spared, of which 4 (0-12) coursed to the right middle/inferior lung lobe. On the left side 10 (3-12) vagus nerve branches were spared, of which 4 (2-10) coursed to the inferior lobe. In 8 cases, lymph nodes were left behind, at stations 10R and 10L while sparing the vagus nerve branches. Lymph nodes at station 7 were always removed.
Conclusions Sparing of pulmonary vagus nerve branches during thoracoscopic esophagectomy is feasible. Extra care should be given to the dissection of peri-bronchial lymph nodes, station 10R and 10L.

Chapter 9. Routes for early enteral nutrition after esophagectomy. A systematic review

Background Early enteral feeding following surgery can be given orally, via a jejunostomy or via a nasojejunal tube. However, the best feeding route following esophagectomy is unclear.
Objectives To determine the best route for enteral nutrition following esophagectomy regarding anastomotic leakage, pneumonia, percentage meeting the nutritional requirements, weight loss, complications of tube feeding, mortality, patient satisfaction and length of hospital stay.
Methods A systematic literature review following PRISMA and MOOSE guidelines.
Results There were 17 eligible studies on early oral intake, jejunostomy or nasojejunal tube feeding. Only one nonrandomized study (N = 133) investigated early oral feeding specifically following esophagectomy. Early oral feeding was associated with a reduced length of stay with delayed oral feeding, without increased complication rates. Postoperative nasojejunal tube feeding was not significantly different from jejunostomy tube feeding regarding complications or catheter efficacy in the only randomized trial on this subject (N = 150). Jejunostomy tube feeding outcome was reported in 12 non-comparative studies (N = 3293). It was effective in meeting short-term nutritional requirements, but major tube-related complications necessitated relaparotomy in 0-2.9% of patients. In three non-comparative studies (N = 135) on nasojejunal tube feeding only minor complications were reported, data on nutritional outcome was lacking. Data on patient satisfaction and long-term nutritional outcome were not found for any of the feeding routes investigated.
Conclusion It is unclear what the best route for early enteral nutrition is after esophagectomy. Especially data regarding early oral intake are scarce, and phase 2 trials are needed for further investigation.

Chapter 10. Routine jejunostomy tube feeding following esophagectomy

Background Malnutrition is an important problem following esophagectomy. A surgically placed jejunostomy secures an enteral feeding route and facilitates discharge with home-tube feeding and long-term nutritional support. However, this is not without complications, and data are lacking that support its use over other enteral feeding routes. For that reason the routine use of jejunostomy tube feeding and routine discharge with home-tube feeding was evaluated with emphasis on the effects on weight loss, length of stay and re-admissions.
Methods Consecutive patients undergoing an esophagectomy for cancer with gastric tube reconstruction and jejunostomy creation between 1-1-2009 and 1-1-2014, were analyzed. Before 1-7-2011 patients were generally discharged when oral intake was sufficient, without tube feeding. Discharge with home-tube feeding was generally performed from 1-7-2011 onwards. Logistic regression analysis corrected for confounders.
Results Some 236 patients were included. The median duration of tube feeding was 35 days. Reoperation for a jejunostomy-related complication was needed in 2%. The median body mass index (BMI) remained stable during tube feeding. The BMI decreased significantly after stopping tube feeding: from 25.6 (1th quartile-3rd quartile 23.0-28.6)kg/m2 to 24.4 (22.0-27.1)kg/m2 at 30 days later (median weight loss: 3.0 [1.0-5.3]kg). The duration of tube feeding or application of home-tube feeding did not affect postoperative weight loss at 90 and 180 days postoperatively. Routine discharge with home-tube feeding did not reduce the admission time (2009: 17 days, 2013: 17 days; P = 0.332) or the readmission rate (2009: 7%, 2013: 10%; P = 0.853).
Conclusion Weight loss following esophagectomy is prevented by routine jejunostomy tube feeding but it occurs the moment that tube feeding is stopped. Discharge with home-tube feeding is not correlated with a reduced length of stay or readmissions. These findings question the value of routine placement of a jejunostomy and emphasize the need for further research.

Chapter 11. Study protocol for the nutritional route in esophageal resection trail: A single-arm feasibility trial (NUTRIENT trial)

Background The best route of feeding for patients undergoing an esophagectomy is unclear. Concerns exist that early oral intake would increase the incidence and severity of both pneumonia and anastomotic leakage. However, in studies including patients after many other types of gastro-intestinal surgery and in animal experiments, early oral intake has shown to be beneficial and enhance recovery. Therefore we aim to determine the feasibility of early oral intake after esophagectomy.
Methods and analysis This study is a feasibility trial in which 50 consecutive patients will start oral intake directly following esophagectomy. Primary outcomes will be the frequency and severity of both anastomotic leakage and (aspiration) pneumonia. Clinical parameters will be registered prospectively and nutritional requirements and intake will be assessed by a dietician. Surgical complications will be registered.
Ethics and dissemination: Approval for this study has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven and the study has been registered at the Dutch Trial Register, NTR4136. Results will be published and presented at international congresses.
Discussion We hypothesize that the oral route of feeding is safe and feasible following esophagectomy as has been shown previously for other types of gastrointestinal surgery. It is expected that early oral nutrition will result in an enhanced recovery. Furthermore, complications related to artificial feeding, such as jejunostomy tube feeding, are believed to be reduced. However, (aspiration) pneumonia and anastomotic leakage are potential risks that are carefully monitored.

Chapter 12. Direct postoperative oral nutrition following esophagectomy is feasible; a multicenter single-arm trial

Background & Aim Direct start of oral intake is considered to be beneficial following most types of gastrointestinal surgery. However, following esophagectomy, most patients are still kept nil-by-mouth since safety and feasibility of early oral intake following esophagectomy is unclear. The Objective is to determine the feasibility and safety of oral nutrition directly after esophagectomy.

Methods Patients (n=50) undergoing minimally invasive esophagectomy were included. Weight loss >15% or pre-existing inability for oral intake were exclusion criteria. Oral nutrition was allowed directly postoperatively. Artificial nutrition was started when <50% of caloric need was met on postoperative day (POD) 5 or when oral intake was impossible. Primary outcomes were pneumonia defined according to the Utrecht pneumonia score and anastomotic leakage according to the Dutch Upper GI Audit criteria. Additionally, all complications graded according to Clavien-Dindo, mortality, ICU stay and hospital stay were registered.

Results Median caloric intake at POD 5 was 58% of required. In 19 (38%) patients artificial nutrition was started, mainly due to complications (n=18). The pneumonia rate was 28% (n=14); 4% (n=2) following aspiration. Anastomotic leakage occurred in 14 %(n=7) patients of whom 6% (n=3) patients required surgery. In-hospital mortality was 2%, 90-day mortality 2%. Median hospital stay was 12 (8-20) days and ICU stay 1 (1-5) days.

Conclusions Direct start of oral nutrition following esophagectomy is feasible and accompanied by complication rates comparable to those reported in literature. However, if complications arise an alternative nutritional route is required.

Chapter 13. Dietary interventions to manage chyle leakage following esophagectomy

Background Chyle leakage often complicates esophagectomy, and may be associated with increased mortality. The objective of this study was to evaluate the management of chyle leakage following esophagectomy and to identify risk factors.

Methods A prospective database of 383 consecutive patients who underwent esophagectomy for cancer between October 2003 and April 2014 was analyzed. Binary logistic regression analysis corrected for confounding factors.

Results Treatment for chyle leakage was initiated in 84 (22%) patients. Independent risk factors for chyle leakage were preoperative BMI <25kg/m² (Odds ratio (OR) 2.1, p=0.010), neoadjuvant chemoradiation (OR 2.5, p=0.002) and transthoracic surgery (OR 5.6, p=0.001). Dietary measures consisting of a medium-chain triglyceride diet (MCT) or total parenteral nutrition (TPN) were the first treatment for chyle leakage in 83 (99%) patients, resulting in leak closure in 73 (87%) patients. The median volume of the chyle leakage that was treated with TPN first was significantly higher during the first 24h after the treatment was initiated (933ml) compared to the median volume of the chyle leakages that were treated with MCT first (550ml). Chyle leakage that was treated first with TPN was significantly associated with need for replenishment of calcium, magnesium and sodium, complications graded Clavien-Dindo grade 3b or higher and mediastinitis and/or empyema. Moreover 30-day/in-hospital mortality was significantly higher (p<0.001) when patients with chyle leakage were treated first with TPN (n=6, 30%) compared to patients treated first with a MCT diet (n=4, 6%) and patients without chyle leakage (n=8, 3%). Independent predictors for 30-day/in-hospital mortality in multivariate analysis were reconstruction using colon (OR 34.0, p<0.001) and chyle leakage that was treated with TPN first (OR 9.7, p=0.003)

Conclusions A transthoracic esophagectomy significantly increases the risk for postoperative chyle leakage. Postoperatively nearly 90% of all chyle leakages can be successfully closed by dietary interventions in the form of an MCT diet or TPN. When TPN was required as first treatment for chyle leakage mortality increased significantly, independent of other factors. This unexpected finding requires further investigation to confirm it and to determine the underlying mechanism.