Risk factors for the development of respiratory complications and anastomotic leakage after esophagectomy

MED-3950 5-årsuppgaven- Profesjonsstudiet I medisin ved Universitetet I Tromsø

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Tromsø 2015

ABSTRACT

Purpose: Exploring potential risk factors for development of two major postoperative complications after esophagectomy.

Methods: A literature review was performed during late 2013 until spring 2015, based on Pubmed searches with the words “anastomotic leakage”, “pulmonary complications”, “risk factors”, “risk stratification”, “esophagectomy“ and associated synonyms. Almost all types of studies were included.

Results: Significant factors found for pulmonary complications were FEV1, ASA score, pulmonary and general comorbidities, lack of physiotherapy, smoking and alcohol consumption, low BMI and sarcopenia, proximal tumor localization, performance status, diabetes and T-stage. Increased blood loss, length of operation and stapler technique, lack of thoracic epidural analgesia, inotrope usage, anastomotic leakage, abdominal complications and not providing enteral feeding by jejunostomy tube. Factors found to increase the likelihood of anastomotic leakage were low S-albumin level, low BMI, high ASA score, arterial calcification, blood loss, not providing omentoplasty, cervical anastomosis, long duration of surgery, posterior placement of the gastric tube, lack of epidural analgesia, respiratory and general complications and delayed gastric emptying.

Conclusion: Several factors were significant for complications after esophagectomy. Some have conflicting results, and need further research. The majority of the results in this study concern general performance, airways and function of the thorax and may therefore affect tissue oxygenation. Preoperative optimization may improve postoperative results.

This subject needs more RCTs and large studies to validate the factors. The causes of these two complications are multifactorial and future research should aim to find risk scores for their development.

INTRODUCTION

The only curative option for resectable esophageal cancer is surgical resection with radical lymphadenectomy, usually after neoadjuvant chemotherapy or chemoradiotherapy (1).

Esophagectomy is associated with high operative risks. Mortality after esophagectomy is below 5 % in high-volume centers (1-3). Esophagectomy imposes surgical trauma, it is perhaps the greatest among general surgical operations. The operation involves the abdomen, chest and neck and it is considered technical and complex with a rather small margin of error. The surgical procedure is also associated with high rates of deaths and complications (4). The occurrence of intraoperative and postoperative complications have also been directly linked to length of stay and postoperative quality of life (5).

Respiratory complications are the most common complication after esophagectomy with incidence rates as high 60 % (5, 6). Respiratory failure, as a result of pulmonary complications is the major cause of morbidity and mortality postoperatively (6). Acute respiratory distress syndrome (ARDS), pneumonia (5-7) and acute lung injury (ALI) are the most severe pulmonary complications (6). Possible explanations for the high incidence of postoperative pulmonary complications are immunosuppression due to the extent of the surgical trauma, postoperative dysfunction of respiratory muscles and poor airway protection (2).

Complications involving the esophagogastric anastomosis are associated with morbidity and mortality. The rate of leakage in a recent systematic review was found to be 0-24% and anastomotic leakage was estimated to be the reason behind 90 % of the deaths after esophagectomy (8). Therefore the quality of the anastomosis may influence the quality of life. Multiple factors can influence the healing of the anastomoses (3). Patient related factors and systemic variables influences anastomotic integrity. This includes medical factors, nutritional status, fluid balance and technical factors during the preparation of the anastomosis (9).

Because of high postoperative mortality and morbidity rates, determining risk factors for major complications after esophagectomy is important in order to make sound evidence based decision when planning the treatment of esophageal cancer. Improvement in this field is essential in order to increase the quality of life in a patient group already struggling with poor prognosis.

The purpose of this literature review is therefore to identify preoperative, peroperative and postoperative risk factors for anastomotic leakage and respiratory complications in patients with esophageal cancer treated with esophagectomy.

METHODS

This is a literature review of major complications occurring after esophagectomy. The review was conducted from the end of 2013 until the spring of 2015. It is based on PubMed search initially using the terms “quality of life”, “esophagectomy”, “complications” and “comorbidities” in the first period of literature search. The search was thereafter narrowed down to “ anastomotic leakage”, “pulmonary complications”, “risk stratification”, “esophagectomy”, “risk factors” and associated synonyms. The focus was to find preoperative, peroperative and postoperative risk factors for the development of pulmonary complications and anastomotic leakage. A total of 72 articles were included in the study. Reviews, meta-analyses, randomized controlled trials, retrospective and prospective studies were included. The articles were published in the period between years 2001 to 2015, with one exception, an article from 1992.

The results are presented as follows:

- Section one: preoperative factors associated with respiratory complications and anastomotic leakage.
- Section two: peroperative factors associated with respiratory complications and anastomotic leakage.
- Section three: postoperative factors associated with respiratory complications and anastomotic leakage.

The discussion section is divided into respiratory complications and anastomotic leakage sections. A discussion is made of the validity of the findings.

<u>The working process</u>

To begin with, a description of the project was designed during a time period of 2 weeks at the end of 2013. The decision was made to undertake a literature study and the subject was decided with some help from the supervisor of the study. The fundamental idea was to find a preoperative risk stratification in patients with esophageal cancer. During the time period of 2 weeks in the summer/autumn 2014 the literature search began. As mentioned above, these searches did not give the results wanted. With some help from the main supervisor, a inspiring paper was found and a narrower approach to this literature study was decided. The idea was to investigate the most common complications after esophagectomy and find risk factors for the development of these complications. During a 3-4 weeks period a new PubMed search was undertaken with the search terms listed above. This approach was successful and a summary of the results from the included articles was made. I discussed the results with my 3 supervisors during the development of the summary and we concluded with another angle of the end product. We narrowed it down to two main complications included in this literature review, pulmonary complications and anastomotic leakage. The goal was now to investigate pre-, per- and postoperative risk factors for the development of the two complication groups. After this conclusion, more focus on the writing and more PubMed search with the same search words were made during the 8 weeks following, with frequent discussion with supervisors.

The project design as a template and during the working progress we narrowed the title down from “preoperative risk stratification in patients with esophageal cancer” to “Risk factors for the development of anastomotic leakage and respiratory complications after esophagectomy”.

RESULTS

Respiratory complications- preoperative factors

Age

A longer life expectancy and aging of the population has led to increased numbers of older patients referred for esophagectomy (10). Age is associated with the development of pleural effusion (11) and pulmonary complications (12-14) by multivariate and bivariate analysis occurring in 25 % of patients older than 75 years compared to 13 % in younger age groups (4).

However, when comparing pulmonary complications in patient groups of > 70 years (17%) and < 70 years (15.3%) the rates were similar. Pulmonary complications were among the most frequent morbidities. Both in-hospital mortality and 30 days mortality were similar in the 2 groups. Not even disease specific 5-years survival differed between older and younger patients (10).

Albumin

No significant association between low preoperative serum- albumin, (< 40) and postoperative pulmonary complications was found (15).

ASA score

A high ASA score was predictive factor for pulmonary complications (12, 13). ASA score of II to IV was significant on multivariate analysis (13).

Preoperative physiotherapy

Not providing respiratory physiotherapy was an independent risk factor for pulmonary complications on multivariate analysis for patients who underwent right thoracic subtotal esophagectomy for squamous cell carcinoma of the thoracic esophagus (16). Physical exercise can optimize performance status and preoperative physiotherapy can prevent decrease in postoperative muscle function. Inspiratory muscle training for two or more weeks before surgery preserves postoperative respiratory muscle strength after esophagectomy (6).

Pulmonary comorbidities and comorbidities in general

Preoperative pulmonary comorbidity was associated with ARDS (11, 17) and pulmonary complications (18). The risk of developing ARDS was 17 times higher in patients with preoperative respiratory disease like recent history of pneumonia, bronchiectasis, pleural effusion, chronic obstructive, chronic bronchitis and chronic asthma (17). Patients with chronic obstructive pulmonary disease (COPD) had more pulmonary complications than patients without COPD. Patients with severe COPD (grade IIB) had more complications than patients with moderate (grade IIA) to mild (grade I). The major complications in the COPD group were pneumonia, atelectasis and prolonged requirements of oxygen supplementation and mechanical ventilation (19).

Patients with cardiac comorbidity prior to esophagectomy, have an increased risk of developing pulmonary complications. Cardiac comorbidity is an independent risk factor for pulmonary complications (18).

Finally, the combination of several comorbidities (smoking, alcohol consumption, cardiac comorbidity, respiratory comorbidity, hepatic comorbidity, renal comorbidity and diabetes) increases the risk of postoperative pulmonary complications (11).

FEV1

An abnormal preoperative FEV1 was significantly associated with ARDS (17), duration of mechanical ventilation (7), pneumonia (20) and is a strong predictor of postoperative respiratory complications (14, 21). 73 % of the patients with ARDS had FEV1 < 70 % of the predictive value (17). 20 % of the patients with respiratory complications had an FEV1 < 60 % (21), patients with a FEV1 less than 65 % were at a significant risk of requiring mechanical ventilation for more than 48 h (7) A FEV1 <75 % was related to with pneumonia (20). Also FVC was significantly associated with duration of mechanical ventilation (7).

Smoking

Smoking has a significant association with the incidence of ARDS (17, 22), pneumonia (11) and respiratory complications (12, 23). A smoking Brinkman index of 800 or more was an independent risk factor for the development of pulmonary complications (15). Brinkman index is defined as the number of cigarettes per day multiplied by years since smoking debut (24).

BMI

No significant association between major pulmonary complications and obesity (BMI of >30 kg/m2) was found (25-29). However, obese patients experience significantly more pleural effusion (29) and one study found obesity associated with longer operating time (28). None the less, obesity did not seem to increase morbidity or mortality after esophagectomy (25).

A low BMI (< 18.5 kg/m2) was significantly associated with the development of ARDS (22) and pulmonary complications (30, 31). Lower BMI also affected overall survival and disease free survival negatively compared to normal BMI (30). Sarcopenia is both a result of cancer and malnutrition. Preoperative pulmonary function was significantly lower in the sarcopenia group and the rate of postoperative respiratory complications were significantly higher. Sarcopenia was considered as a risk factor for pulmonary complications (32). Inadequate nutrition can lead to malnutrition, associated with expiratory muscle weakness and pulmonary complications after major upper abdominal surgery (6).

Neoadjuvant chemotherapy and chemoradiotherapy

Neoadjuvant chemoradiotherapy is significantly associated with respiratory failure in need of mechanical ventilation beyond 24 h (33), ARDS (33), pneumonia (34) and pulmonary complications (15). Chemoradiotherapy was also correlated with duration of mechanical ventilation and hospital length of stay (7). The respiratory complications were directly linked to death (33). The total amount of lung spared from doses of 5 or more Gy was an independent inverse risk factor for pulmonary complications (35). Another study showed that the incidence of ARDS and pneumonia significantly increased when 40 % or more of the lung volume received 10 Gy or more (6).

Other studies showed the opposite results with no statistical significance when comparing neoadjuvant chemoradiotherapy with surgery alone (36-38). Comparing neoadjuvant chemoradiotherapy combined with surgery and surgery alone showed no significance in postoperative respiratory complications (39).
In a meta-analysis of 23 randomized controlled trials, no increase of postoperative respiratory complications was identified when comparing both neoadjuvant chemotherapy and chemoradiotherapy with surgery alone (40). In addition, no difference between neoadjuvant chemotherapy and chemoradiotherapy regarding respiratory complication was found (40). In a second study, no difference in respiratory complications was found when comparing neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy. Despite this, complications were significantly more severe among patients who underwent preoperative chemoradiotherapy than chemotherapy and a trend towards an increased incidence of respiratory complications was shown (41).

However, postoperative complications after preoperative chemoradiotherapy were more than twice as likely to develop in patients with squamous cell carcinoma as patients with adenocarcinoma. It was more likely, for the same patient group, to develop respiratory complications (42).

T stage
Advanced tumor stage (T3 and T4 vs. T1 and T2) was found to be associated with respiratory complications on a bivariate analysis in a longitudinal cohort (12).

Tumor localization
Proximal tumor localization was found to be a significant independent predictive factor for pulmonary complications (4).

Performance status
Performance status was found to be an independent variable associated with pulmonary complications on multivariate analysis (14).

Diabetes
Diabetes was found to be a strong predictor of pulmonary complications on multivariate analysis (23).

Alcohol consumption
Alcohol was a significant preoperative risk factor for respiratory complications on a multivariate analysis (23).

Scoring system
A scoring system has been developed to predict postoperative pulmonary complications; it includes age, performance status, FEV1% and DLCO (14);

Table 1

Score:	1 point	2 points	3 points	4 points
Age:	51-60 years	61-70 years	71-80 years	> 80 years
FEV1%	80-89.9%	70-79,9 %	60-69,9 %	< 60 %

Table 1: A summary of the scoring system (14).

These two variables were added to the performance status value to achieve a final score. Using 4 as cutoff value, the accuracy of prediction of pulmonary complications was 65,4% (14). An external validation of this risk score concluded with the scoring system as a reliable instrument. The scoring system can be used during the preoperative period to predict patients with higher risk of getting postoperative pulmonary complications (38).

Anastomotic leakage- preoperative factors

Albumin

Serum- albumin (s-albumin) level had a significant association with development of anastomotic leak (43, 44) in patients who underwent cervical esophagogastric anastomosis with a gastric tube interposition. The study recommends S-albumin levels over 32g/L to reduce the hazard of anastomotic leak (43). Another study found a significant association between low S-albumin and major complications on postoperative day 3 and 7 as well as anastomotic leak. An interesting finding in the study was that albumin combined with CRP and white cell count could create a so-called “Nun score”. A score of > 10 was predictive for anastomotic leakage and death on postoperative day 4 (44).

Comorbidities

A preoperative history of diabetes was associated with increased rates of anastomotic leakage during esophagogastrectomy with gastric tube interposition and cervical esophagogastric anastomosis, although not reaching significance (43). Both cardiac comorbidity like congestive heart failure and hypertension and renal insufficiency were significantly associated with anastomotic leakage in a large study that used data from The Society of Thoracic Surgeons Database (45). Other comorbid conditions, including diabetes, pulmonary disease and cardiovascular conditions that required medical therapy, were identified as a risk factor for developing anastomotic leakage (46).

BMI

Low body mass index (BMI < 17) was related to leakage in patients with locally advanced esophageal cancer who underwent esophagectomy (20). Malnutrition has been found to be associated with an increased rate of anastomotic failure (47).

In a meta-analysis of BMI and postoperative complications, higher BMI was significantly associated with an increased risk of anastomotic leakage (27). The definition of obesity was a BMI over 30 and this patient group had an increased risk of anastomotic leak in patients with adenocarcinoma (29). The risk of anastomotic leak increased with higher BMI, from 12.5% in underweight (BMI<18.5) to 27.6% in obese patients. No statistical significance between BMI groups was shown regarding length of stay, long-term survival and prognostic value (48).

In another meta-analysis the results showed that diabetes in obese patients, but not obesity alone was associated with a significant impact on the risk of anastomotic leakage

and also atrial fibrillation (49). Obesity was associated with longer operating time but not with anastomotic leakage after minimal invasive esophagectomy. However, obese patients had higher prevalence of diabetes, a lower prevalence of peripheral vascular disease and lower prevalence of stage III disease than the non-obese group (28).

Finally, one study found that obese patients had no increased risk of anastomotic leakage (25).

Neoadjuvant chemotherapy and chemoradiotherapy

In a large study that used data from The Society of Thoracic Surgeons Database, 50 % of the patients who underwent esophagectomy were treated with preoperative chemotherapy and 45 % underwent preoperative radiotherapy. The study found no statistical association between neoadjuvant therapy and postoperative anastomotic leakage (45). The same results were observed when comparing neoadjuvant chemoradiotherapy with surgery alone (36, 39). In a meta-analysis of 23 randomized controlled trials, no increase of postoperative anastomotic leakage was identified when comparing both neoadjuvant chemotherapy and chemoradiotherapy with surgery alone. In addition, no difference between neoadjuvant chemotherapy and chemoradiotherapy regarding postoperative anastomotic leakage was found (40). In yet another randomized study, no statistic significance was shown for anastomotic leakage when comparing neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy (41).

ASA score

ASA score III to IV is a predictive factor of leakage on multivariate analysis (13).

Calcification of arteries

Both minor and major aortic calcifications and also calcification of the right postceliac arteries were found as independent risk factors for anastomotic leakage after esophagectomy. Preoperative routine CT images for the presence of calcification in the aorta, right postceliac arteries, celiac axis and the left postceliac arteries were reviewed (50).

Respiratory complications – peroperative factors

Minimal Invasive Esophagectomy (MIE)

Total minimal invasive esophagectomy reduces the risk of respiratory failure (11) and pulmonary complications (18) whereas open esophagectomy increases the risk of respiratory complications on a bivariate analysis in a longitudinal study (12). A prospective RCT study showed significant reduction of pneumonia by minimal invasive approach (1). However, other studies have shown that thoracotomy during the operation is not associated with an increased risk of respiratory complications (23). Length of hospital stay is reduced after MIE (1, 18).

Length of the operation

A long operating time was significantly associated as a predictive factor for development of pneumonia (20) and pulmonary complications (4, 23, 32) in patients undergoing esophagectomy. The operating time significantly increased with MIE approach (1, 51).

Blood loss
Blood loss greater than 630 ml was found to be an independent risk factor for pulmonary complications in patients who underwent right thoracic subtotal esophagectomy for squamous cell carcinoma of the thoracic esophagus (16). Blood loss/ body weight was also an independent risk factor for the development of pulmonary complications on multivariate analysis (15). Volume of blood loss was significantly reduced in total minimal invasive (1, 18, 51) and hybrid minimal invasive esophagectomy (18).

Steriods
Steroids can reduce the incidence of pulmonary complications (6, 16, 52). A preoperative single dose of methylprednisolone 10 mg/kg can reduce postoperative pulmonary complications. This dose was tried in a randomized study where one group was administered methylprednisolone 10 mg/kg 30 minutes before surgery. The effect was significantly lower organ system failure (33% vs 61% in the control group). Significantly fewer in the methylprednisolone group had cardiovascular failure and respiratory failure. The duration of mechanical ventilation was 3 days compared to 5 days in the control group. Prophylactic methylprednisolone in this study reduced the incidence of postoperative pulmonary failure and instability of cardiac function and also overall morbidity. The improvement of respiratory function was related to shorter duration of mechanical ventilation (52).

However, a systematic review and meta-analysis of 7 RCT studies and 4 interventional non-randomized studies showed that there was no significant effect of glucocorticoids. Despite this result, a subgroup analysis identified the most promising dosing regimen for further research. The dose is weight-dependent of methylprednisolone 10 to 30 mg kg^{-1} within 30 minutes preoperatively (53).

Technique of the anastomosis
In a systematic review and meta- analysis stapler and hand-sewn techniques were analyzed. The stapler technique increased the absolute risk significantly for pulmonary complications postoperatively in 8 % (54).

Anastomotic leakage- peroperative factors

Intraoperative blood loss
Intraoperative blood loss can increase the risk of anastomotic leakage (43, 55), in cervical anastomoses with a gastric tube. Reduced tissue oxygen tension is the presumed mechanism (43).

In a systematic review and meta- analysis the stapler and hand-sewn technique on the anastomosis were analyzed. Results showed that the stapled technique generated less blood loss when compared to the hand-sewn technique. The stapled technique also generated less surgical time compared with hand-sewn (54).

Suture technique

Running suture technique was significant in the development of anastomotic leakage in a retrospective study with cervical esophagogastric anastomosis with a gastric tube interposition (43). A manual technique was significant on multivariate analysis as a predictive factor for anastomotic leakage (13). In a randomized prospective study the findings were in favor of the stapled technique, as it was superior in preventing anastomotic leakage compared

to hand-sewn technique and resulted in shorter operating time (56). However, other studies have found no significant difference between hand-sewn and stapled anastomosis groups. Again the results from other studies are conflicting. No evidence of significant difference of anastomotic leakage and mortality between hand-sewn and stapled anastomoses was found in a meta-analysis of 8 randomized studies and the same results were shown in another randomized meta-analysis of 10 randomized studies (8, 9, 54). The superiority of either hand-sewn or stapled techniques cannot be definitively established and we have to consider them as equal (8).

Omentoplasty

Omentoplasty is an efficient method to decrease the incidence of anastomotic leakage (57, 58). A randomized study compared omentoplasty with non- omentoplasty for the prevention of anastomotic leakage. It showed that the technique had significantly lower occurrence of postoperative leak in the omentoplasty group. This result includes both cervical and thoracic anastomosis. However, there was no statistically significant difference between the two groups in terms of mortality, recurrence after surgery or pulmonary complications (58). When sleeve wrapping the pedicled omentum around the anastomosis, the technique both lowered postoperative leakage rate and had a shorter recovery period. The anastomotic leakage was managed conservatively with enteral nutrition and it closed spontaneously in 10 days (59).

Type of resection

In a large study that used data from The Society of Thoracic Surgeons Database, the type of resection correlated with the risk of postoperative anastomotic leakage. On univariate analysis the anastomotic leakage rate was 12,3 % for patients with cervical anastomosis, compared with intrathoracic anastomosis which had 9,3 % in rate of leakage (45).

Cervical anastomosis increases the risk of postoperative anastomotic leakage after esophagectomy (36, 55). A systematic review and meta-analysis of 4 randomized trials showed that cervical anastomosis was associated with higher risk of anastomotic leakage than thoracic anastomosis. The incidence was significantly different between groups with a anastomotic leakage of 26 % in the cervical group and 4 % in the thoracic group, but no difference in mortality was found. A cervical anastomosis was also significantly more associated with recurrent nerve trauma (60). Another meta-analysis reported similar results (9).

Another study found that anastomotic complications are more common after gastric- rather than colonic reconstruction, for both late and early complications (46).

Length of the operation

In a large study that used data from The Society of Thoracic Surgeons Database, the length of the operation for more than 5 hours was associated with increased risk of postoperative anastomotic leak (45).

Epidural analgesia

Thoracic epidural analgesia are used to reduce postoperative pulmonary complications, it has also been reported to improve the bowel microcirculation and therefore to prevent

postoperative anastomotic insufficiency. A retrospective study showed that thoracic epidural analgesia might decrease the risk of anastomotic leakage (55).

Minimal Invasive Esophagectomy (MIE)
A meta-analysis of 12 studies showed no statistic significance between minimal invasive and open esophagectomy in terms of the incidence of anastomotic leakage (9). However;
one meta-analysis showed significantly less anastomotic leakage in hybrid –minimal invasive technique, a technique using either thoracoscopic or laparoscopic, in comparison to open esophagectomy (51).

Posterior mediastinum placement of gastric tube
A posterior placement of the gastric tube had significant association with development of anastomotic leakage during esophagogastrectomy with gastric tube interposition and cervical esophagogastric anastomosis (43).

Respiratory complications- postoperative factors

Analgesia
Thoracic epidural analgesia reduces the risk of respiratory failure, overall pulmonary complications and mortality. It also facilitates early extubation (6). The risk of postoperative respiratory failure was significantly reduced in patients who had thoracic epidural analgesia (11).

Inotropes
The use of inotropes in the intraoperative and in a 30 – day period after surgery was significantly associated with ARDS (17).

Anastomosis
Postoperative breakdown of the anastomosis had a high odds ratio for the development of postoperative ARDS in patients who underwent two-phase esophagectomy, with one lung ventilation in the second phase (22). Anastomotic leakage was an independent risk factor for the development of postoperative pulmonary complications (13, 18).

Abdominal complications
Abdominal complications were a significant predictive factor for pulmonary complications on multivariate analysis (13).

Jejunostomy tube
An early start of a jejunostomy tube for enteral feeding after esophagectomy has been shown to reduce the rate of postoperative pneumonia with 50 % or more, compared to fasting or parenteral nutrition (6).

Anastomotic leakage-postoperative factors

Jejunostomy tube

Lack of a jejunostomy tube was significantly associated with anastomotic leakage in a study of cervical esophagogastric anastomosis with a gastric tube interposition (43).

Gastric emptying during the postoperative period

Delayed gastric emptying during the postoperative period had significant relationship with development of anastomotic leakage during esophagogastrectomy with gastric tube interposition and cervical esophagogastric anastomosis (43).

Cardiac complication

The incidence of atrial arrhythmia and requirements for inotropic support are higher in patients who have anastomotic leakage than those who do not (61). Patients with anastomotic leakage had significantly more frequently postoperative atrial arrhythmia, ventricular arrhythmia and deep venous thrombosis (45).

Respiratory complications

The incidence of respiratory failure, bronchopneumonia and ventilator support were significantly higher in the patients group with anastomotic leakage (61). Anastomotic leakage was significantly associated with pneumonia, ARDS, re-intubation and empyema (45). The development of ARDS was associated with increased risk of anastomotic leakage postoperatively (55).

Other complications

Postoperative sepsis and renal failure was associated with postoperative anastomotic leakage in a large study that used data from The Society of Thoracic Surgeons Database. The length of stay was significantly increased in patients with anastomotic leakage- 13.1 days for patients without anastomotic leak and 27.4 days in the patients with anastomotic leak (45). Ischemia of the conduit predisposes for anastomotic leakage (46).

Table 2

Complication	**Preoperative**	**Peroperative**	**Postoperative**
Pulmonary complications	- FEV1 - ASA score - Preoperative pulmonary comorbidity - Comorbidities in general - Not providing preoperative physiotherapy - Smoking - Low preoperative BMI and sarcopenia - Proximal tumor localization - Performance status - Diabetes - Alcohol consumption - T stage	- Increased blood loss - Length of the operation - Stapler technique	- Lack of thoracic epidural analgesia - Use of inotropes - Anastomotic leakage - Abdominal complications - Not providing early enteral feeding by a jejunostomy tube
Anastomotic leakage	- Albumin - Comorbidities - Low BMI - ASA score - Calcification of arteries	- Intraoperative blood loss - Not providing omentoplasty - Cervical anastomosis - Length of the operation - Posterior placement of the gastric tube	- Epidural analgesia - Respiratory complications - Complications in general (sepsis, renal failure and ischemia of the conduit) - Delayed gastric emptying

Table 2: Summary of the significant factors unanimously showing an increased risk of pulmonary complications and anastomotic leakage.

DISCUSSION

Respiratory complications

Common major respiratory complications found in our study are pneumonia, ARDS and respiratory failure. This literature review confirmed several factors increasing the risk of pulmonary complications from the preoperative to the postoperative period. Many of the preoperative factors found significant for the development of pulmonary complications are factors easy to evaluate in the preoperative period.

FEV1 is easy evaluated by spirometry, this study showed FEV1 to be a significant preoperative risk factor for pulmonary complications. We have to remember that accurate results from spirometry are technique dependent. Preoperative pulmonary comorbidities such as COPD were also a risk factor in this study. This is normally evaluated by spirometry.

An evaluation by a physiotherapist and preoperative physiotherapy to prepare for the operation is also an easy preparation before surgery. It is important to optimize function with respiratory training by a respiratory physician. Many of the patients with esophageal cancer have a smoking history with a potential reduction in pulmonary function, this makes the preoperative optimization of respiratory function even more important (16). Smoking as a preoperative risk factor can be evaluated by the Brinkman index, the number of cigarettes per day multiplied by years since smoking debut (24). Results in this study showed a Brickman index of 800 or more as a significant factor.

Age was a significant preoperative risk factor for the development of pulmonary complications on multivariate analyses. Another study found opposite result when comparing groups of older than 70 years and younger than 70 years. The improvements are likely a result of surgical technique and perioperative care. A recent review concluded with that age is not a valid exclusion criterion. Well-selected patients, based on proper preoperative assessment, can survive with acceptable postoperative morbidity (2). The selection whether to proceed with surgery has to be made based on comorbidities reasons rather than age. Both smoking and alcohol consumption are found as risk factors in this study. There is a correlation between patients with cancer esophagus and consumption of alcohol and tobacco. The possibility for higher total consumption is greater in older patients due to longer exposure to alcohol and tobacco and thus higher risk of comorbidities related to these lifestyle factors.

There it is a correlation between the increased incidence of adenocarcinoma and prevalence of obesity. Surgery may be more risky because of the increased incidence of cardiopulmonary comorbidities (2). There is a belief among many surgeons that there is an increased difficulty with technical challenges and postoperative complications in obese patients undergoing surgery (25). However, from the results of this study, obesity alone is not a risk factor for esophagectomy.

Many of the patients are malnourished as a result of reduced food intake, because of a malignant stenosis (21). Improvement of performance status is important to reduce pulmonary complications, both in the pre- and postoperative phase. Malnutrition is associated with expiratory muscle weakness leading to pulmonary complications. Fewer complications are observed when intensive nutritional support is given to patients undergoing esophagectomy, but clear evidence is lacking. Nutrition plays an important role in in the pre- and postoperative phase in esophagectomy. It has been showed that early enteral nutrition after gastrointestinal surgery improves patient recovery and reduces morbidity and mortality (6).

Chemoradiotherapy is not a direct risk factor for the development of postoperative respiratory complication, but a trend towards more severe complications has

been shown following this treatment. Survival after surgery alone is poor with a 5-year survival of 15-25 % and there is a significant benefit of 13 % at 5 years after neoadjuvant chemoradiotherapy (34). The results, from this literature review suggest that chemoradiotherapy is a risk factor for the development of ARDS. A possible explanation for this severe complication after the treatment is that it can provoke radiation pneumonitis and together with another massive insult, like surgery, cause cytokine release and damage lung tissue (62). Some studies suggest that lower doses of radiotherapy leads to a minimized irritated lung volume. These findings can be a factor to reduce possible pulmonary complications, although the positive effect of the therapy must still be beneficial. One of these studies practiced pulmonary function tests 4 weeks after completed neoadjuvant therapy. This allows a recovery period and control of function prior to surgery (38).

However, neoadjuvant chemoradiotherapy had no significant association to increased postoperative pulmonary complications and this result also includes neoadjuvant chemotherapy (40, 41). These two studies have the most promising results and a conclusion from this is that both neoadjuvant chemotherapy and chemoradiotherapy are not considered as risk factors for respiratory complications. More randomized studies are needed to get a clear picture if neoadjuvant therapy increases complications. The different result from the retrospective studies may be explained by different neoadjuvant regimens in terms of schedule or doses for both chemotherapy and radiotherapy (34). We have not controlled for this in our literature review.

The scoring system (table 1) developed to predict pulmonary complications seems promising for the preoperative period. Including age, performance status, FEV1% and DLCO (14). The three first factors are found in our study as risk factors for pulmonary complications. This finding also confirms the earlier discussion about age combined with comorbidities and the importance of preoperative spirometry test. This scoring system needs further evaluation and has potential for the clinical practice.

Minimal invasive surgery reduces factors associated with pulmonary complications, like blood loss, pain and inflammation; the question is if it reduces pulmonary complications directly. There is no conclusive evidence of the benefits of MIE over OE, because of the lack of RCTs (51). More randomized studies are needed; the conclusion from the results of this literature review is that minimal invasive surgery is a good technique to reduce pain, blood loss and in-hospital stay.

There is a consistent trend in decreased blood loss (1, 63) and a slight trend of shorter hospital stay after minimal invasive surgery (63). Compared to open surgery, patients undergoing minimal invasive surgery report less pain in the first ten days post-surgery (64). This literature review found increased blood loss to be an independent risk factor for pulmonary complication; Minimal invasive surgery can have an indirect effect of pulmonary complications and can be beneficial for the short-term quality of life. The surgeon learning curve for MIE has a definitive impact on outcome and a lot of experience is required before mastering MIE. Increased operator experience has shown decrease in operating time, conversion rates and complications in general (63). Interesting factors for further research is the position during the surgery. Is there a difference between prone or left semilateral position and can one of them reduce pulmonary complications (1, 6)? Putting the mediastinum in the habitual position and thereby relieving the chest and abdomen of compression, the use of prone position in minimal invasive surgery might be beneficial compared to the lateral position (1).

The results considering steroids are conflicting and more randomized studies are needed. Findings from this literature review suggest that the administration of methylprednisolone 10 to 30 mg kg^{-1} administered within 30 minutes preoperatively may be beneficial (52, 53).

Analgesia is important after esophagectomy. Postoperative pain results in less mobilization, compromising pulmonary function and coughing. It can result in atelectasis and pneumonia. Thoracic epidural analgesia is more effective than intravenous opioids (6). The technique is easy to apply after the surgery and is important for the prognosis of complications.

As mentioned in the results, inotropes are significantly associated with ARDS. Inotropes cause alveolar vasoconstriction and this might predispose ischemic lung injury and be the cause that leads to ARDS (17).

The result of an anastomotic leakage is acid secretion from the gastric fluid. The anastomosis is located in the negative pressured thorax which easily draws gastric fluid through anastomotic sutures or staple lines (65). The results from this literature review of a correlation between postoperative anastomotic leakage and pulmonary complications is easy understood if the tissue inside the thorax is contaminated by gastric fluid resulting in tissue damage.

Anastomotic leakage

The main groups of factors related to anastomotic leakage are esophageal factors, patient related factors and surgical or technical factors. The esophagus anatomy does not consist of a serosal layer and is mainly composed by longitudinal muscles contributing to insufficient suture strength (47, 65). Both the absence of serosa and the presence of a longitudinal layer necessitates gentle maneuvers during anastomosing to avoid tears and damage (65). In this literature review, there was no significant association concerning suture technique and the development of anastomotic leakage, when looking at randomized studies. Several reports found decreased rates of leakage with stapled anastomoses, whereas others have not showed difference between stapled and mechanical technique. When discussed in a meta-analysis where the non-randomized were excluded, there was no significant difference between stapled and mechanical. From this we can conclude that importance lies in gentle maneuvers and the best technique cannot be definitively established at this time. We have to consider them as equal (8).

Inadequate blood supply, absence of serosa and the tension across anastomotic site are three previous established risk factors for anastomotic leakage (58). Two meta-analyses (9, 60) have found cervical anastomoses as risk factor for anastomotic leakage and this review was not able to find any contradicting results. The cervical anastomosis is placed under greater tension and has a bigger risk of ischemia in the conduit than thoracic anastomosis, because of the compromised vascular integrity resulting in a greater breakdown and leakage (9, 58). Omentoplasty has shown promising results with a reduction of anastomotic leakage. It is a technique of wrapping the greater omentum around a gastrointestinal anastomosis, in hope of decreased incidence and severity of anastomotic leakage. The omentoplasty group significantly reduced the duration of hospitalization. It was considered as a safe and effective technique (58). The conclusion from this is that not using omentoplasty is a peroperative risk factor for postoperative anastomotic leakage.
The function of the omentum is to seal microscopic leakage and remodel tissue. It includes neovascularization and localizes potential malignant inflammatory process in the tissue. The technique and function of the omentum seems promising in our literature study. The technique is also effective in the higher risk cervical anastomoses and use of omentoplasty is therefore utilized in this group. It is a minor modification of surgical technique. The sleeve wrapping technique also managed the leak conservatively and closed the leakage spontaneously in 10 days with enteral nutrition (59). Reoperation is always a risk for the

patients in general. Taking this into consideration, the sleeve wrapping technique seems promising.

Many of the risk factors resulting in higher leakage appear to compromise the vascular supply to the anastomosis. Modifying these factors further may help to reduce the morbidity and mortality (45).

Adequate blood supply is a major factor for the healing process (66). The surgeon has three alternatives for the conduit; Using the colon, the stomach or the jejunum as a conduit. The majority of surgeons use the stomach (3, 65). (Figure 1) The result is an entire vascularization depending on the right gastroepiploic artery, 60 % of the gastric tube is supplied by the right gastroepiplocic artery and the remaining 40 % of the stomach that is distal to the pyloric end depends on the supply from the submucosal network of small vessels (3, 47, 65). Contributing to a decreased blood flow in the upper part of the gastric tube, compared to the antrum and corpus, even if the hemodynamic is stable (50).

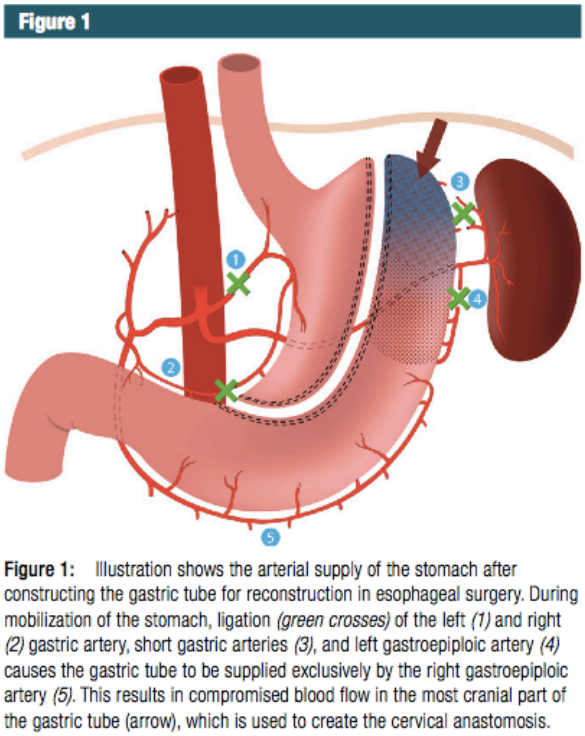

Figure 1: Illustration shows the arterial supply of the stomach after constructing the gastric tube for reconstruction in esophageal surgery. During mobilization of the stomach, ligation *(green crosses)* of the left *(1)* and right *(2)* gastric artery, short gastric arteries *(3)*, and left gastroepiploic artery *(4)* causes the gastric tube to be supplied exclusively by the right gastroepiploic artery *(5)*. This results in compromised blood flow in the most cranial part of the gastric tube (arrow), which is used to create the cervical anastomosis.

Figure 1:(50)

Comorbidities like diabetes, cardiovascular and pulmonary disease, with potential to affect the blood supply to the conduit are found significant in this study. Also a high ASA score, as a summary of the performance and comorbidities, was found significant.

Intraoperative factors found significant were blood loss. The result in this study showed the importance of adequate blood supply then the vascular anatomy isn't optimal. Hypotension during and after the surgery can be of potential negative impact for perfusion and tissue oxygenation, and must therefore be avoided (3). This literature review found no statistic significance between open or minimal invasive surgery in term of anastomotic leakage. Like reported for pulmonary complications, the blood loss was less in the minimal invasive group. A potentially positive factor for anastomotic leakage and can indirectly have a positive effect. Further studies are needed.

Epidural analgesia has been reported to improve the bowel circulation and therefore potentially preventing anastomotic insufficiency. However, epidural analgesia is also known to lower systemic vascular tone and hence blood pressure and therefore decreasing perfusion of the anastomosis, which in turn may affect anastomotic healing. Further evaluation of this is needed. The positive effect of epidural analgesia for postoperative pulmonary complications is known and a pulmonary complication seems more severe and more common than anastomotic leakage. The positive effect of analgesia in pulmonary complications weighs up for the potential unknown risk for anastomotic leakage at this period of time. The use of epidural analgesia makes it possible for more evaluation and studies. This is interesting for further analysis.

In a recent review, a new technique of using indocyanine green fluorescence angiography and Doppler examination to evaluate blood supply and assist in construction of the gastric conduit was applied. Comparing leakage before and after introduction, rate went from 20 % to 0 %. No difference in the operating team was observed. The conclusion was a dramatic decrease of anastomotic failure (66).

Preoperative CT images for evaluation of calcification of arteries is a new and promising risk factor for further research. CT imaging is normally a part of the preoperative evaluation in every patient, which makes this risk factor easy evaluated. An independent risk score to grade the calcification is required in the evaluation. This needs further research. Both minor and major aortic calcifications and also calcification of the right postceliac arteries are independent risk factors for anastomotic leak after esophagectomy. Like mentioned earlier, healing of the anastomosis is essential in leakage prevention. The most cranial part of the gastric tube has a decreased blood supply, even when the hemodynamics are stable the blood supply is compromised. Atherosclerosis is a known cause of ischemia and can compromise the vascular supply of the gastric tube. A combination of generalized vascular disease by aortic calcifications, and local perfusion by postceliac arteries calcifications is likely the mechanism for ischemia and anastomotic leakage (50).

Adequate oxygen delivery can be a problem in the postoperative period especially if the patient gets respiratory failure. Adequate wound perfusion, gastric construction and oxygenation are important for wound healing in the anastomosis (55). Respiratory complications are significantly associated with anastomotic leakage in the postoperative period from the results in this study. Postoperative pulmonary complications can result in bad oxygenation of the tissue in the anastomosis. Preventing postoperative pulmonary complications also prevents anastomotic leakage.

Our study found albumin as a preoperative risk factor for anastomotic leakage. Recommendation of serum albumin levels over 32 g/L to avoid anastomotic leakage has been found in one of the studies. Despite this finding, preoperative albumin levels correlated more with mortality (67-69). Patients who survived the first year had higher preoperative albumin (67) and patients with S-albumin levels of more than 3.5 g/dl had fewer postoperative complications (68). In general, pre-therapeutic serum albumin is both an inflammatory and nutritional indicator (70). Hypoalbuminemia is common in cancer patients, especially in those with cancer in the digestive tract. Hypoalbuminemia is attributed to increased catabolism, obstruction of the esophagus and ongoing inflammatory process (70). The measure of S-albumin can be done from the preoperative period to the postoperative period. It is accurate, simple and cheap. Factors for error in the evaluation of serum albumin in the clinical practice are proinflammatory cytokine, capillary permeability, hepatic disease and drugs. The clinician must take this into consideration when evaluating the serum albumin level. More studies are needed; the results are not strong considering albumin levels, with findings from two previous studies. From the few results of malnutrition and low preoperative BMI found in this study, the conclusion of an increased risk of postoperative anastomotic leakage can be made. More randomized studies are needed.

It is easy to calculate BMI according to WHO definitions. Overweight and obese patients may have reduction in residual capacity and expiratory reserve volume and the excessive fatty tissue has low regional oxygen tension and may predispose to impaired wound healing (48, 71). These two factors may cause lack of healing of the anastomosis. The findings in our study are contradictive regarding obesity. Findings of both significance, and that obesity not alone increased the risk of postoperative complications such as anastomotic leakage, but obesity combined with diabetes did. Length of stay and long-term survival were similar between BMI groups and had no prognostic value (48). Obese patients had

significantly better long-term survival than patients who weren't obese (49). These facts are also important when making a risk analysis.

When discussed if obese patients are suffering from more recurrence after surgery, significant reduction in the total number of nodes removed in the high BMI has been found earlier. Obese undergo unsuccessful lymphadenopathy; this may result in more frequent metastases and recurrence (72). This statement has been disproved with no difference of harvest lymph nodes between high and low BMI groups, also with no increased morbidity and mortality in super obese patients with BMI > 35 when compared with lower BMI groups (25). With these findings higher BMI groups are not in higher risks than other.

We are able to conclude with that obesity alone is not an independent risk factor for surgery. Even tough the results are conflicting, with two meta-analyses with the opposite results. The importance lies in if the overweight patients have diabetes or other comorbidities. This needs further investigations.

Limitations:

The inconsistent results highlight the limitations of non-randomized studies. This is particularly a problem when it comes to selection bias. In this study, all types of articles are included. Many of the results are from retrospective studies. This is a clear and large limitation in this study. Although significant, some of the results mentioned in this literature review are based on one or few studies. This is a weakness regarding the strength of the results.

We have not selected results after the histological type of tumors; the results are mixed between histological types. We haven't selected for ethnicity or location in the world. This can also be a limitation.

There has been a lack of definition of an anastomotic leakage in earlier studies. As a result of the lack of definition, the incidence can vary widely and difficulties of comparing results are present (3, 47). A common definition has to be used in future studies to provide more accurate results. We have not evaluated the definition of anastomotic leakage in our study. A review of anastomotic complications (47) are proposing the adapted definition by Leirut and associates (3) as the most applied and promising for further use in subject evaluation.

CONCLUSION

Several factors have been found to be significant for both pulmonary complications and anastomotic leakage, the majority of which affect the patients general performance status, the airways and function of the thorax and therefore possibly affecting tissue oxygenation. Optimizing these factors can be beneficial for the postoperative result.

Anastomotic leakage is often caused by compromised vascularization of the gastric conduit. Cervical anastomosis was a well-evaluated risk factor for anastomotic leakage. Interesting findings for further analyses are the recent studies found about arterial calcification and the use of peroperative green fluorescence angiography and Doppler examination.

Preoperative assessment and reduction of postoperative pulmonary complications is difficult due to reduced general status and organ dysfunction in patients with esophageal carcinoma. Based on the findings in this literature review it seems vital to evaluate patients with preoperative pulmonary function tests and to optimize respiratory function with the aid of a physiotherapist. The decision weather to perform surgery cannot be based merely on age and BMI, but many risk factors combined may guide the decision making towards

palliative treatment. Nutrition is important for this group of patients to optimize muscle function and more investigation in this field is needed. The most important part in the preoperative phase is function of the lungs and comorbidities. The preoperative risk score (table 1) seems promising and may be taken into use.

In general, this field of surgery needs more RCTs and large studies to test the validity of the factors. If possible, also more meta-analyses are needed. The causes of these two complications are multifactorial and future research should aim to find risk scores for the development of these complications.

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