Preoperative selection and conditioning of patients with esophageal cancer

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Primary Objectives:This study consist of:1) a prospective cohort study in which all patients with esophageal cancer, selected for esophagectomy, and willing to be included in this cohort, are followed to assess their complications, short en long…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON36289

Source
ToetsingOnline

Brief title
Selection in esophagectomy

Condition

- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal therapeutic procedures

Synonym
oesophaguscarcinoom

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Esophagectomy, Selection, Surgery, Ventilation technique

Outcome measures

Primary outcome

Main study parameter/endpoint for prospective cohort study and pilot RCT

Prospective cohort study:

Immunological response (TNF-α, CRP, FABP, procalcitonine, IL-1, IL-2, IL-6, IL-8, IL-10 and chemokine receptors (CXCR1/CXCR2)) as predictor for the following parameters/endpoints:

1. Complications:

Pulmonary complications; respiratory insufficiency, acute respiratory distress syndrome (ARDS), pneumonia, atelectasis, pleural effusion, empyema and pulmonary embolism.

Cardiac complications; arrhythmia and myocardial infarction.

Other major complications; subphrenic abscess and/or intra-abdominal abscess, systemic inflammatory response syndrome (SIRS), sepsis, anastomotic leakage, chylothorax, renal failure, liver failure and ileus.

2. Short-term outcome: postoperative mortality, hereby defined as death within 90 days after esophagectomy or any death during admission in hospital where the resection was performed.

3. Long-term outcome: patients without postoperative mortality will be selected and only cancer related death cause will be scored. Death of any other cause will be scored as end of follow up

4. The estimates will be adjusted for the following patients* and tumour characteristics: age, use of neo-adjuvant therapy, comorbidity, ASA-classification, POSSUM score and TNM classification.

Pilot RCT:

Differences in immunological response between HFJV and conventional ventilation, analyzed by using following concentrations: TNF-α, CRP, FABP, procalcitonine, IL-1, IL-2, IL-6, IL-8, IL-10 and chemokine receptors (CXCR1/CXCR2).

Secondary outcome

Prospective cohort study

To explore the value of polymorphism at TNF-α gene locus (TNF-α genotype 308) as a useful predictor of preoperative risk assessment for mortality and morbidity after esophagectomy.

Pilot RCT

1. Differences in complications between HFJV and conventional ventilation:

Pulmonary complications; respiratory insufficiency, ARDS, pneumonia, atelectasis, pleural effusion, empyema and pulmonary embolism.

Cardiac complications; arrhythmia and myocardial infarction.

Other major complications; SIRS, sepsis, anastomotic leakage.

2. To investigate differences in frequencies of death within 90 days after esophagectomy or any death during admission in hospital where the resection was performed between HFJV and conventional ventilation.

3. To investigate whether there are differences between both breathing techniques (conventional vs HFJV) in the conduct of the operation (blood loss, operation time) and recorded intraoperative anesthesiologic variables: BIS (bispectral edge), cardiac output measurements (using PICCO (Puls Contour Cardiac Output)), transcutaneous CO2 (TcCO2) measurement, ROS, EVLW (extra-vascular lung water) and ITBV (intrathoracic blood volume).

Study description

Background summary

Treatment of esophageal cancer
Esophageal cancer is a highly lethal disease with an overall 5-year survival rate of approximately 20% (1). The incidence in the Netherlands (1800 pts) is increasing rapidly in the last three decades, especially due to chronic reflux esophagitis in patients with obesity and Barrett related reflux disease. An increased incidence is also observed in the elderly population with a peak shifting towards the 65-70 years. Currently, promising treatment methods, such as neo-adjuvant chemo-radiation and tyrosine kinase inhibitors, are emerging with frequently reported complete responses (25-30%). Nevertheless, surgery remains the primary curative option.

Disadvantages of treatment
However, esophagectomy as a high-risk complex surgical procedure has severe postoperative complications of around 35-50% and a relatively high rate of postoperative mortality between 3% and 15%. The most common complications are respiratory (40%-50%) ranging from atelectasis / pneumonia to respiratory failure (ARDS and acute lung injury) often accompanied by sepsis. Besides respiratory complications, cardiac complications are also common with a frequency of 15-20%, mostly due to cardiac arrhythmias (2).

Risk analysis
Preoperative risk stratification for postoperative mortality and morbidity may help patients and families address the magnitude of both the disease and the therapy. It is pivotal for both the patient and the surgeon to realistically assess the magnitude of the surgical insult. So far a reliable individual risk analysis stratification to guide surgeons and oncologists in the decision-making is missing and it should be done in the context of an overall clinical judgment. Until now, selection is based on patient*s characteristics,

comorbidity index, including mental and physical condition, and tumor staging with CT/EUS and PET/CT.
With a more appropriate risk-prediction, which would be partly based on the immunological status of the patient, we might be able to identify patients with high estimated morbidity and mortality. A careful selection based on a more advanced immunological status may be helpful in the implementation of an individual treatment strategy and to perform adequate preoperative interventions to reduce postoperative complications.

Immunological response

The surgical trauma during esophagectomy and necessity of one lung ventilation, using double lumen endotracheal intubation, cause early activation of leucocytes, macrophages and endothelial cells with enhances expression and release of anti- and pro-inflammatory cytokines (TNF-α, CRP, FABP*s, procalcitonine, IL-1, IL -2, IL-6, IL-8, IL-10) and chemokine receptors (CXCR1/CXCR2). The acute phase response, consisting of an initial release of TNF-α, IL-1 and IL-6 the so-called primary mediators of acute stress, occurs within 30-60 minutes with a sharp increase after 2-4 hours and a maximum of 24/48 hours after the surgical trauma. A local response of IL-1 stimulates the synthesis and release of IL-2 by CD4+ T-helper lymphocytes, the cell mediated immunity, leading to an overall systemic effect. Interleukin 10 is the most important anti-inflammatory cytokine and inhibits pro-inflammatory cytokine secretion of IL-1, IL-6 and TNF-α from monocytes, macrophages and Th1 (T-helper) cells. Furthermore, the Fatty Acid Binding Proteins (FABPs) plays an important role in activating the immune system by TNF and insulin and may be used as a potential serum marker for systemic inflammatory response syndrome (SIRS).

Significance of elevated cytokine concentrations

Patients with an elevated concentration of cytokines have an increased risk of renal failure, myocardial and respiratory dysfunction (14, 22, 23). In addition, there appears to be a positive correlation between IL-6 and the impact of the surgical procedure (operating time, blood loss, amount of fluid administered) (11). So, the levels of primary cytokines could be used as a prognostic marker in relation to the development of early and serious complications. Moreover, they also may have a potential negative correlation with the one-and 5-year survival in these patients. (12)

Factors affecting the immune response

Surgery generally has a negative impact on the immunological status of surgically explored patients. However, patients diagnosed with esophageal cancer have a severe increased risk of impaired immunological response. The cause of an impaired immunologic response is different and several patients* characteristics could be responsible for a decreased immunological reaction. For example: advanced age (>70 years), a high comorbidity risk profile, the use of neo-adjuvant chemo-radiation and anesthetic factors including the method and

duration of intubation (one-lung ventilation). Research is needed to determine the significance of these characteristics in the immunological status of the individual patient. Reducing the systemic stress response could be an important contribution to avoid morbidity and mortality, but may also affect long-term survival as was reported in some studies. (3-10,12)

Additional to the above systemic effects several other factors are to consider affecting the immunological response. Differences in response may also be related to:

1. Cytokine genotyping of the patient.
SIRS, which occurs in each patient after an esophagectomy, is accompanied with an elevated TNF-α production by monocytes increased level of FABPs and expression of IL-6. FABPs maintain membrane integrity by protecting the cell from the detergent effects of excess non-protein bound fatty acids. They facilitate the transport of fatty acids and other lipid mediators throughout the cell and as a potential central regulator of common pathways controlling inflammatory and regulating metabolic signaling. Polymorphism of TNF-α gene locus in particular 308 (TNF-α genotype 308), which is also observed in other critically ill patients, is associated with an increased mortality and poor prognosis and can be analyzed in our surgical laboratory (21). Therefore, screening of this high-risk group seems to be appropriate.
2. Prolonged intubations and re-intubations also induce SIRS and are associated with postoperative respiratory morbidity. Patients participating in a preoperative respiratory physiotherapy program (Intensive Muscular Training (IMT), will develop a greater vital lung capacity by increasing their skeletal muscle mass. The effect of this intervention may be observed in our study as well.

Intervention
3. Oxygenation
During esophagectomy, the surgeon explores the esophagus usually with a right sided thoracotomy in case of a mid esophageal tumor or trough a left sided approach in the case of a distal tumor. Both procedures require one-lung ventilation (OLV) for an optimal approach. Routinely, a double lumen tube is used for that purpose, with pressure controlled ventilation on the ventilated lung. Pressure controlled ventilation with low tidal volumes (and higher PEEP values) lead to a reduction of mortality in patients with ARDS (13). The benefit of this strategy seems to be a reduction of the sheer stress of the alveoli, thereby attenuating the inflammatory responses associated with mechanical ventilation.
Nevertheless, even with the use of lung protective ventilation (i.e. low tidal volumes) during esophageal resection, there is still a high respiratory morbidity up to 49%. While some of this morbidity is related to a ventilator-induced injury of the continuously ventilated lung, respiratory morbidity may also be the consequences of the lung collapse on the surgical side for a relatively long period. Besides, there is growing evidence that an

early inflammatory response might represent the final pathway that heralds the onset of respiratory complications. (14)

High Frequency Jet Ventilation
A potential method of avoiding and attenuating some of the associated complications with OLV may be obtained by the use of High Frequency Jet Ventilation (HFJV) on both lungs (15-16). It provides adequate oxygenation with only small tidal volumes, thereby reducing sheer stress on the non-exposed lung and preventing complete collapse of the exposed lung. The surgeon should be able to retract the exposed lung sufficiently to enable a good surgical view of the esophagus without causing collapse and atelectasis of the lung. HFJV is characterized by high frequency (>100/min) ventilatory cycles and very low tidal volumes.

Literature
In a recent published article, Buise et al (17) concluded that HFJV for both lungs, using a single-lumen tube, is a safe and adequate ventilation technique during esophagectomy. HFJV had no significant influence on the incidence of postoperative pulmonary complications, but reduced the perioperative blood loss and led to a lower need for fluid replacement. However, Buise et al failed to test HFJV compared to the immunological status of the patient and especially the cytokines concentrations during surgery. In a randomized trial of Misiolek et al (18) in which 29 patients receiving HFJV and 31 patients receiving one-lung ventilation, they concluded that HFJV is a safe and comparable option of ventilation for open-chest thoracic procedures. Ender et al (19) concluded that HFJV could be safely used during minimal invasive coronary bypass graft surgery with a reduction in the peak inspiratory pressure (from 32.1 ± 5.9 to 10.0 ± 2.8 mbar), but at a cost of a rise in $PaCO_2$. Finally, Moloney et al (20) described in a review article none significant differences in complication rates between conventional ventilation and HFJV. There appears to exist a safely use of HFJV in respect to oxygenation. These authors do speculate however over a study design whereby these two types of ventilation should be compared in relation to cytokine concentrations. Based on these results and our own experience in the UMCG, the anesthetic department considers the use of HFJV as a safe method, which can be used as a proven method in thoracic surgery.

Study objective

Primary Objectives:
This study consist of:
1) a prospective cohort study in which all patients with esophageal cancer, selected for esophagectomy, and willing to be included in this cohort, are followed to assess their complications, short en long term outcome in relation to their immune response.
2) a pilot randomized clinical trial that is performed within this cohort including all patients with an ASA <=2, that are willing to participate.

The aim of the prospective cohort study is to analyze the impact of immunological response during treatment of patients with esophageal cancer who are selected for esophagectomy on complications, short and long-term outcome in the context of patients* and tumour characteristics. Preoperative risk stratification for postoperative mortality and morbidity may help patients and families address the magnitude of both the disease and the therapy.

The aim of the pilot randomized clinical trial (pilot RCT) is to explore whether High Frequency Jet Ventilation (HFJV), as a strategy to decrease the anesthesiological stress by improving oxygenation compared to the standard double lumen technique, can reduce the inflammatory stress response during esophagectomy.

Secondary Objectives:
Prospective cohort study
- To explore the value of polymorphism at TNF-α gene locus (TNF-α genotype 308) as a useful predictor of preoperative risk assessment for mortality and morbidity after esophagectomy.
- To investigate the added value of the immunological response as a predictor for mortality and morbidity in combination with known risk models, such as the ASA-classification and the POSSUM.

Pilot RCT
- To investigate whether there is a relation between both breathing techniques (conventional vs HFJV) and the conduct of the operation (blood loss, operation time), (severity of) complications (especially pulmonary) and in hospital and/or 90 day mortality.
- To investigate differences between HFJV and conventional ventilation with recorded intraoperative anesthesiologic variables: BIS (bispectral edge), cardiac output measurements (using PICCO (Puls Contour Cardiac Output)), transcutaneous CO2 (TcCO2) measurement, ROS, EVLW (extra-vascular lung water) and ITBV (intrathoracic blood volume.

Study design

Prospective cohort study
Blood samples (10ml) will obtained via venapunction during the entire hospital admission at various predetermined moments (see overview for details). Immediately after extraction, blood samples will be centrifuged at 14.000 rpm for 10 minutes. Sera and plasma will be separated and samples will be stored in aliquots at -70 degrees. Cytokine levels will be measured using specific enzyme-linked immunosorbent assays (ELISAs). For all tests commercially ELISA's en Western Blots are available. The following concentrations will be measured by an ELISA analysis: TNF-α, CRP, FABP, procalcitonine, IL-1, IL-2, IL-6, IL-8, IL-10 and chemokine receptors (CXCR1/CXCR2) and the real time PCR genotyping will be determined.

Overview of blood sampling:

• 1e blood sample: prior for the start of neo-adjuvant treatment
• 2e blood sample: day 7 of neo-adjuvant treatment therapy
• 3e blood sample: prior for the start of participation of IMT study
• 4e blood sample: prior to the start of operation
• 5e blood sample: during two lung ventilation
• 6e blood sample: during one lung ventilation
• 7e blood sample: end of surgery
• 8e blood sample: first day at ICU (12-24 hours after end of surgery)
• 9e blood sample: second day at ICU (between 24 and 48 hours after surgery)
• 10e blood sample: between 48 and 72 hours after the arrival on the oncology department
• 11e blood sample: between 48 and 72 hours after the last blood sample

Note: The period of neoadjuvant treatment is 5 weeks, followed by a rest period of 5-6 weeks before surgery is performed. The average treatment is 14 weeks, while the average ICU stay is 2 days and 2 weeks on the surgical department.

Pilot RCT: HFJV
Patients who agree to participate in the prospective cohort study will be asked to participate in the intervention study as well (provided an ASA <= 2). Patients who decide to participate will be randomized to receive either traditional ventilation or HFJV. Randomization will be performed by the Trial Coordination Center (TCC) of the UMCG.

Oxygenation
Conventional ventilation will consist of 6-8 ml/kg/breath, at approximately 12 breaths/min to achieve an end tidal CO2 of 4.0-5.0 kPa. Intubation will be occurred with an appropriately sized double lumen tube (female 37/39, male 39/41) for OLV and its position will be confirmed with a bronchoscope. HFJV will be based on PaCO2 during tumor resection. A standard single lumen tube will be inserted. These patients will receive HFJV of both lungs. During surgery all measurements are continuously recorded by the RUGLOOP II data logging system.

Blood samples will be taken during surgery on predetermined moments (see overview), at the start of operation, during two-lung ventilation, during one-lung ventilation (or during HFJV) and at the end of operation. Blood samples will be stored in aliquots at -70 degrees.
Concentrations of TNF-α, CRP, FABP, procalcitonine, IL-1, IL-2, IL-6, IL-8, IL-10 and chemokine receptors (CXCR1/CXCR2) will be determined by an ELISA.

Study burden and risks

Prospective cohort study

As hematological testing is performed on a frequent basis anyway in patients with esophageal cancer burden and risks are neglect able. Frequent vena punction carries limited risks and is usually well tolerated.

Pilot RCT
We expect a decreased inflammatory response in patients who are randomized in the HFJV group, which could be a benefit for an individual patient.
Based on data from literature and our own experience in the UMCG, the anesthetic department considers the use of HFJV as a safe method, which can be used as a proven method in thoracic surgery. Unforeseen complications or difficulties with the use of HFJV during esophagectomy will come clear during this pilot study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All patients selected for a curative intended esophagectomy.
Patients >18 years with a given informed consent
Histological proven esophageal or GEJ cancer (adeno/squamous cell)
ASA class 2 or less (only for HFJV study)

Exclusion criteria

Patients who are mentally disabled or incapable to give informed consent
Patients with severe (bullous) emphysema (only for HFJV study)
ASA class 3 or more (only for HFJV study)

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2011
Enrollment:	100
Type:	Actual

Medical products/devices used

Generic name:	Medical Ventilator: High Frequency Jet Ventilation
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-06-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	27-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL34554.042.10