Respiratory complications after oesophagectomy for cancer

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Summary
Surgery is the cornerstone of treatment for resectable tumours of the oesophagus. Recent advances in surgical techniques and anaesthesiology have led to a substantial decrease in mortality and morbidity. Respiratory complications affect about 30% of patients after oesophagectomy and 80% of these complications occur within the first five days. Respiratory complications include sputum retention, pneumonia and ARDS. They are the major cause of morbidity and mortality after oesophageal resection and numerous studies have identified the factors associated with these complications. The mechanisms are not very different from those observed after pulmonary resection. Nevertheless, there is an important lack of definition, and evaluation of the incidence is particularly difficult. Furthermore, respiratory complications are related to many factors. Careful medical history, physical examination and pulmonary function testing help to identify the risk factors and provide strategies to reduce the risk of pulmonary complications. Standardized postoperative management and a better understanding of the pathogenesis of pulmonary complications are necessary to reduce hospital mortality. This article discusses preoperative, intraoperative, and postoperative factors affecting respiratory complications and strategies to reduce the incidence of these complications after oesophagectomy.

Key words: Oesophagectomy • Oesophageal Cancer • Pulmonary Complications • ARDS • Pneumonia.
Introduction

In France, oesophageal cancer contributes 5% of all malignancies in males and less than 1% in females, with 8000 new diagnoses each year. Oesophageal cancer ranks fourth among causes of death from cancer. Although oesophageal cancer is an uncommon disease whose overall incidence has remained stable for the last two decades, its epidemiological profile has changed in recent years. Thus, epidermoid cancer, which chiefly affects men with a history of heavy smoking and drinking, has declined substantially. Adenocarcinoma of the distal oesophagus, in contrast, arises from foci of Barrett’s oesophagus related to gastrooesophageal reflux and is becoming more common, with a 6-fold incidence increase over the last 20 years. These epidemiological trends (fewer epidermoid carcinomas and more adenocarcinomas) have been recorded throughout Europe and in most occidental countries. They may be ascribable to changes in risk factor profiles. Decreased use of alcohol and tobacco largely explains the declining incidence of epidermoid carcinoma. The rising incidence of adenocarcinoma seems ascribable to known risk factors, namely, gastrooesophageal reflux, Barrett’s oesophagus, obesity, and Helicobacter pylori infection.

Surgery remains the reference standard for the treatment of early-stage oesophageal cancer that seems resectable. The surgical procedure, which is standardized, involves en-bloc oesophagectomy with lymph-node dissection. A 1980 literature review by Earlam and Cunha-Melo showed 30% postoperative mortality, with less than 5% of patients alive after 5 years [1]. Ten years later, another literature review indicated a reversal of the risk/benefit ratio, the postoperative mortality rate being halved and the 5-year survival rate quadrupled (to about 20%) [2]. Since then, advances in surgical techniques, anaesthesia, and intensive care have provided further substantial decreases in postoperative mortality rates. Progress made in diagnosing and staging the disease, early-stage diagnosis in high-risk populations, and greater aggressiveness of the treatments used have improved the life expectancy of patients with oesophageal cancer. At present, high-volume centres have postoperative mortality rates in the 5%-10% range and a 5-year survival rate of nearly 35% [2-3].

The most common adverse events after surgery for oesophageal cancer are respiratory complications, which constitute the leading cause of postoperative death. These complications are similar to those seen after lung resection surgery, share the same mechanisms, and require the same preventive measures. Many studies have investigated the pathophysiological mechanisms of respiratory complications after oesophageal cancer surgery (RC-OCS). A major obstacle to effective studies is the lack of standardized definitions of RC-OCS, which hinders comparisons of incidence rates across studies. RC-OCS are multifactorial: they depend on baseline patient-related factors and co-morbidities, peri-operative factors related to the surgical procedure and anaesthesia, and postoperative factors related to management in the intensive care unit.

This review draws on recently published data to discuss the factors involved in the pathogenesis of RC-OCS and to suggest preventive strategies.

Epidemiology and incidence of respiratory complications

Incidence

The incidence of RC-OCS varies across studies depending on the study design and definitions used. In some studies, RC-OCS were defined based on therapeutic criteria, such as the use of interventions in addition to the standard treatment [4] or the need for and duration of postoperative ventilatory assistance, whereas other studies used an ICU stay longer than 5 days [5, 6]. The lack of standardized definitions of RC-OCS precludes valid comparisons of incidence rates across studies (table I). Thus, the rates of RC-OCS and pneumonia vary up to 2-fold depending on the definition used. Furthermore, few studies assessed RC-OCS rates in patient populations that were homogeneous in terms of the surgical approach, surgical technique, use of induction therapy, and other factors. Nevertheless, the RC-OCS rate was between 10% and 25% in most studies [5-8]. In practice, when standardized definitions are used, 39% of patients experience RC-OCS, which cause 60% of hospital deaths. Among RC-OCS, nearly 80% occur early, within the first 5 postoperative days.

Definitions

The most reliable definition of surgical complications relies on a classification scheme comprising five severity grades [9]. This widely used scheme can be applied to all surgical procedures, by incorporating the specific features of each (table II). A major strength of the scheme is the use of general terms to group all possible complications into categories. Furthermore, ICU management is taken into account, which constitutes an improvement over many earlier classification systems. This “objective” classification scheme can serve to compare quality of care across centres, skill levels, and therapeutic strategies.

Nevertheless, this five-grade classification scheme does not help to describe or to understand the mechanisms of RC-OCS. Indeed, it fails to separate respiratory complications that are related to the technical aspects of the surgical procedure from respiratory complications due to other factors. In complications related to technical aspects, structural
damage caused during surgery affects respiratory function, as a result of the intrathoracic location of the oesophagus; complications in this group include anastomotic leakage, tracheobronchial fistula, and recurrent laryngeal nerve palsy.

The other group of postoperative respiratory complications is related to multiple factors such as preoperative respiratory function, co-morbidities, the quality of respiratory preparation, the surgery per se and its indication, the anaesthesiological management, and the ICU management. These two groups of complications – structural and non-structural – are lumped together in most of the available studies. For didactic reasons, we will discuss these two groups separately, although the underlying pathophysiological mechanisms are often intertwined.

Table I.
Respiratory complications in published case-series of oesophagectomy patients

<table>
<thead>
<tr>
<th>References</th>
<th>Patients</th>
<th>RC-OCS (%)</th>
<th>Pneumonia (%)</th>
<th>ARDS/ALI (%)</th>
<th>Re-intubation (%)</th>
<th>In-hospital death (%)</th>
<th>ICU stay (days)</th>
<th>Hospital stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karl [7]</td>
<td>143</td>
<td>19</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>2.1</td>
<td>3.3</td>
<td>13.5</td>
</tr>
<tr>
<td>Doty [8]</td>
<td>120</td>
<td>8</td>
<td>2.5</td>
<td>2.5</td>
<td>nc</td>
<td>0.8</td>
<td>nc</td>
<td>15</td>
</tr>
<tr>
<td>Chandrashekar [10]</td>
<td>76</td>
<td>22</td>
<td>13</td>
<td>9.2</td>
<td>9</td>
<td>2.6</td>
<td>3</td>
<td>nc</td>
</tr>
<tr>
<td>Fang [11]</td>
<td>441</td>
<td>7.3</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>3.9</td>
<td>nc</td>
<td>nc</td>
</tr>
<tr>
<td>Atkins [12]</td>
<td>379</td>
<td>15.8</td>
<td>15.8</td>
<td>nc</td>
<td>6.1</td>
<td>5.8</td>
<td>nc</td>
<td>nc</td>
</tr>
<tr>
<td>Ferguson [6]</td>
<td>292</td>
<td>27</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>13.7</td>
<td>nc</td>
<td>19</td>
</tr>
<tr>
<td>Avendano [5]</td>
<td>81</td>
<td>36.1</td>
<td>32.8</td>
<td>9.8</td>
<td>nc</td>
<td>11.5</td>
<td>6.1</td>
<td>17.7</td>
</tr>
</tbody>
</table>

nc: not communicated; RC-OCS: respiratory complications after oesophageal cancer surgery; ICU: intensive care unit

Table II.
Classification of complications after major surgery. Definitions and adaptation to the respiratory system. (From Dindo et al. [9]).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Respiratory system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions</td>
<td>Secretion retention or atelectasis requiring physiotherapy</td>
</tr>
<tr>
<td>Grade II</td>
<td>Any deviation from the normal postoperative course requiring pharmacological treatment with drugs other than such allowed for grade I complications</td>
<td>Pneumonia treated with antibiotics on the ward</td>
</tr>
<tr>
<td>Grade III</td>
<td>Any deviation from the normal postoperative course requiring surgical, endoscopic, or radiological intervention</td>
<td>Suction during bronchoscopy</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anaesthesia</td>
<td></td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Intervention under general anaesthesia</td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication requiring IC/ICU management</td>
<td></td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis)</td>
<td>Respiratory failure requiring endotracheal or non-invasive ventilation</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorgan dysfunction</td>
<td>Respiratory failure with failure of another organ (kidney)</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient</td>
<td>Death</td>
</tr>
</tbody>
</table>

IC, intermediate care; ICU, intensive care unit
Non-structural respiratory complications

Respiratory complications that are unrelated to structural tissue damage during surgery constitute a continuum of three stages of the same pulmonary disease process, which unfolds during the postoperative period. The mildest stage is bronchial secretion retention and the most severe is acute respiratory distress syndrome (ARDS). Each stage is potentially reversible, and early appropriate ventilatory assistance (non-invasive ventilation [NIV]) with bronchoscopic aspiration may prevent progression from one stage to the next.

Bronchial secretion retention and atelectasis

Impaired lung ventilation is often reported after oesophageal surgery, with rates of 2% to 60% depending on the study [5-14]. In some studies, atelectasis or secretion retention was considered an adverse event if bronchoscopy or NIV was required to reopen the blocked lung territory and/or to improve blood gas values. These complications do not meet the criteria for nosocomial pneumonia: there is no fever or leukocytosis. However, they can be viewed as the earliest stage of a lung disease that requires measures aimed at preventing progression to pneumonia. They usually occur within 72 hours after surgery.

Nosocomial pneumonia

Nosocomial pneumonia is the most common RC-OC-S. The standardised definition [15] requires the development of a radiological infiltrate at least 48 hours after admission and the presence of at least two of the following criteria: purulent sputum, temperature >38.5°C or <35°C, and leukocytes >10,000/mm³ or <1500/mm³. Ventilator-associated pneumonia (VAP) is nosocomial pneumonia occurring after at least 48 hours of mechanical ventilation, even if the lung parenchyma was inoculated during surgery. Two groups of nosocomial pneumonia can be distinguished based on the time to occurrence and association with mechanical ventilation [16] (Table III). This distinction is of considerable prognostic significance, as delayed VAP is strongly associated with hospital death. Whenever possible, VAP should be documented using a reliable bacteriological sampling technique such as protected-specimen brush sampling [17] or another microbiological method [18]. VAP usually develops 2 to 6 days after surgery.

Acute respiratory distress syndrome (ARDS)

ARDS is the most severe of all RC-OC-S and still carries a high mortality rate. In this non-cardiogenic pulmonary disease, the value of the PaO₂/FiO₂ ratio is used to differentiate ARDS strictly speaking from acute lung injury (ALI), whose incidence is far from negligible. ARDS/ALI occurs in up to 14% of patients after oesophageal cancer surgery and is fatal in about half the cases. A meta-analysis of over 60,000 patients showed that ARDS occurred in 27% of patients after transthoracic oesophageal resection compared to 13% after transhiatal resection [19]. Appropriate fluid and electrolyte management during the perioperative period is crucial, as lymph resorption by the lung is diminished by 50% after oesophagectomy [4]. ARDS is rare after the fifth postoperative day. Patients with ARDS require ICU admission and specific therapeutic interventions (e.g., nitric oxide and prone positioning). The identification of microorganisms is often difficult and requires specialized techniques (protected aspiration, bronchoalveolar lavage, or lung biopsy).

Table III.

Differences in nosocomial pneumonia affecting non-ventilated and ventilated patients (ventilator-associated pneumonia, VAP). From Ewig S. et al. [16].

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Aetiology</th>
<th>Mortality</th>
<th>Diagnosis</th>
<th>Antibiotics</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ventilated patients</td>
<td>Relatively low</td>
<td>GNEB, <em>Legionella</em> spp</td>
<td>Probably relatively low</td>
<td>Clinical; sputum; virtually no data on bronchoscopy</td>
<td>Monotherapy &lt;5 days; Combination if &gt;5 days</td>
</tr>
<tr>
<td>Ventilated patients</td>
<td>High</td>
<td>Core pathogens; PDRM</td>
<td>30-50%</td>
<td>Clinical; TBAS; bronchoscopy</td>
<td>Early onset: monotherapy; Late onset: combination therapy</td>
</tr>
</tbody>
</table>

ARDS is the most severe of all RC-OC-S and still carries a high mortality rate. In this non-cardiogenic pulmonary disease, the value of the PaO₂/FiO₂ ratio is used to differentiate ARDS strictly speaking from acute lung injury (ALI), whose incidence is far from negligible. ARDS/ALI occurs in up to 14% of patients after oesophageal cancer surgery and is fatal in about half the cases. A meta-analysis of over 60,000 patients showed that ARDS occurred in 27% of patients after transthoracic oesophageal resection compared to 13% after transhiatal resection [19]. Appropriate fluid and electrolyte management during the perioperative period is crucial, as lymph resorption by the lung is diminished by 50% after oesophagectomy [4]. ARDS is rare after the fifth postoperative day. Patients with ARDS require ICU admission and specific therapeutic interventions (e.g., nitric oxide and prone positioning). The identification of microorganisms is often difficult and requires specialized techniques (protected aspiration, bronchoalveolar lavage, or lung biopsy).

Respiratory complications due to structural damage during surgery

The complications in this group are directly related to the surgical technique. Any postoperative respiratory event should prompt a search for these structural complications. Structural complications should not be included in analyses of the incidence or risk factors of non-structural complications.

Simple pleural effusions

Development of a pleural effusion is the rule on the side of the thoracotomy and is common on the other side. Pleural effusions cannot be classified among respiratory complications. However, the contralateral effusion consistently
aggravates the disturbances in ventilatory mechanics and therefore requires prompt drainage. The fluid is usually a serofibrinous or blood-tinged exudate. Bile-tinged or purulent fluid should prompt an evaluation for infection or anastomotic leakage.

**Anastomotic dehiscence and leakage**

Intrathoracic anastomotic fistula is the most serious complication of oesophageal cancer surgery. The rate of occurrence is less than 10% [13]. Infections and nutritional deficiencies may develop, leading to substantial mortality. Risk factors may include longer length of the reconstruction with ischemia, compression, and above all distension of a retrosternal reconstruction. Therefore, continuous drainage and gastric tube patency must be monitored closely in the early postoperative period. The mean time from surgery to leakage is 6 days, with a range of 4 to 10 days. The presenting manifestations may be signs of infection (fever and pneumonia) or local signs (discharge to the skin or through the chest tube). The diagnosis rests on the detection of gastrointestinal fluid at the neck or in the chest tube. Other manifestations that should suggest a fistula consist of an isolated fever, acidosis, pneumonia refractory to optimal treatment, and unexplained isolated acute respiratory failure. Complications of fistulas include lung abscesses, mediastinitis, and septic shock.

**Haemothorax and chylothorax**

Haemothorax is an uncommon complication that may require surgery for bleeding control or clot removal. The bleeding source is an injury to the mediastinum, chest wall, or spleen. Chylothorax, which is seen in 0.5% to 2% of patients, is related either to a thoracic duct injury or to inadequate lymphorrhagia control and occurs in 0.5% to 2% of patients [13]. The chylous effusion develops within the first few days after surgery. Chylothorax occurs chiefly after extensive node dissection and often requires repeat surgery.

- Respiratory complications after oesophageal cancer surgery (RC-OCS) occur in 30% of patients and, among them, 80% develop within the first 5 days.
- RC-OCS account for nearly 60% of hospital deaths.
- Non-structural RC-OCSs consist of bronchial secretion retention, pneumonia, and ARDS. They should be distinguished from RC-OCS caused by structural tissue damage inflicted during surgery.

**Etiopathogenesis of respiratory complications after oesophageal cancer surgery**

The multiple factors that promote the development of RC-OCS [5-14] include patient-related factors (poor baseline ventilatory performance, smoking, poor nutritional status, and induction therapy) and perioperative factors (operating time, mechanical ventilation, and thoracotomy). In addition, several postoperative factors such as analgesics and fluid management may be involved. These “macro-events” emphasize the usefulness of the protective measures that are widely implemented in high-volume centres such as the use of intraoperative fluid management protocols, early extubation, postoperative epidural analgesia, and NIV.

**Preoperative factors**

**Patient age**

Patient age is not considered a strong predictor of poor outcomes. Thus, patients younger and older than 70 years had similar rates of 5-year survival and respiratory morbidity [20-22]. After oesophagectomy, patients older than 75 or 80 years show no increase in the RC-OCS rate but are at increased risk for cardiovascular events (e.g., arrhythmia or heart failure). Older age is one of three covariates in a scoring system for predicting the risk of pulmonary and cardiovascular complications after oesophageal cancer surgery [6].

**Absolute or relative immunodepression, malnutrition**

Few patients exhibit cachexia or a rapid decline in general health at the time of surgery, since preoperative treatments are now available for decreasing tumour bulk, thereby allowing the resumption of enteral nutrition. Nevertheless, malnutrition can lead to muscle wasting, most notably at the diaphragm [23]. A multivariate analysis on data from a case-series of 102 oesophagectomy patients showed that a preoperative serum albumin level less than 39 g/L independently predicted the occurrence of postoperative respiratory complications [24]. In addition, malnutrition is associated with immune system impairments, which increase the risk of infection, an effect that may be amplified by the use of chemotherapy. In a case-series of 103 patients who had oesophageal cancer managed with oesophagectomy, the preoperative nutritional status influenced the postoperative course [25]. Preoperative malnutrition was associated with significant decreases in cellular immune responses [25]. Cellular immunity can be restored by providing adequate nutrition.

**Preoperative respiratory function**

Respiratory function impairment before surgery is probably the most widely implicated factor in the occurrence of RC-OCS. In many studies involving multivariate analyses, a decrease in the forced expiratory volume in 1 minute (FEV1) before surgery was independently associated with the
development of complications [6, 26]. Common causes of respiratory function impairment include a history of smoking [13], failure to quit smoking before surgery, and overweight. The presence of non-reversible respiratory function impairments may be the strongest predictor of RC-OCS. The wisest course often consists in postponing surgery to allow effective bronchial preparation and at least 3 to 6 weeks without smoking. Smoking cessation is promptly followed by decreases in coughing and sputum production and by a substantial increase in the preoperative FEV₁ value. Patients with respiratory failure or chronic obstructive lung disease (COPD) should undergo polysomnography to look for sleep apnoea syndrome. In this indication, including NIV in the respiratory preparation programme is clearly beneficial. In all likelihood, tests for bronchial bacterial colonization would prove valuable in patients with respiratory function impairments. Among patients undergoing lung resection, nearly 40% had bronchial colonization by pathogenic bacteria detected by examination of the intraoperative tracheal aspirates [27]. The most common colonizing bacteria may show limited susceptibility to widely used antimicrobial agents. Bronchial bacterial colonization is a patient-related factor that may serve as the lead point for an infectious process culminating in the development of nosocomial pneumonia.

**Neoadjuvant chemoradiotherapy**

The current treatment of oesophageal cancer involves a multidisciplinary management strategy that rests on neoadjuvant chemoradiotherapy. Nearly 50% of surgically treated patients receive neoadjuvant chemoradiotherapy. Although induction therapy was associated with higher hospital mortality rates in several studies [5, 28, 29], many studies found no unequivocal association between chemoradiotherapy and RC-OCS [30].

Radiation therapy, depending on the dose, can damage the lung parenchyma or pleural membranes and increases the risk of structural surgical complications. The RC-OCS rate is closely associated with the irradiated tissue volume. The incidence and severity of RC-OCS increase with the radiation dose. Higher radiation doses are also associated with a greater decline in the diffusion capacity of the lung for carbon monoxide [28].

Chemotherapy contributes to induce systemic immunodepression and to increase the risk of postoperative infection. Thus, the identification of unusual bacteria or viruses in postoperative lung biopsy specimens was more common after chemoradiotherapy [31]. In a study of preoperative bronchoalveolar lavage fluids collected after neoadjuvant chemoradiotherapy, we found bronchial colonization in 30% of patients [32]. Both bacteria and viruses (cytomegalovirus) were identified. Preoperative administration of antimicrobials against these micro-organisms was associated with a decreased risk of ARDS in the group of patients managed with preoperative bronchoalveolar lavage [32].

**Intraoperative factors**

**General anaesthesia, ventilatory mechanics, and prophylactic antimicrobials**

General anaesthesia alters the ventilation/perfusion match, as well as thoracopulmonary volumes and compliance. These effects are related both to the supine position and to muscle relaxation. They produce ventilatory disturbances or atelectasis, particularly in dependent areas. These abnormalities are aggravated by diaphragmatic dysfunction due to reflex inhibition of the phrenic nerve input, which is probably unrelated to pain, as epidural opioid injection fails to improve diaphragmatic function. Epidural administration of local anaesthetics is needed to decrease the diaphragmatic dysfunction, and the effect is only partial [33]. The diaphragm remains hypotonic for several hours or even days as a result of either reactive neurogenic stunning or injury during surgery (stretching, compression, or phrenotomy). When a thoracotomy is performed also, chest wall rigidity is an additional factor. In combination, these factors cause a restrictive defect that persists for over 2 weeks but is particularly marked during the first week. These factors, together with gastrointestinal tract distension related to postoperative ileus, diminish the effectiveness of coughing.

The prophylactic antimicrobial agents used in patients receiving oesophageal cancer surgery are first- or second-generation cephalosporins. Recent studies documented cases of postoperative pneumonia due to microorganisms that were not covered by the prophylactic antimicrobials. Thus, in many instances, efficacy of the recommended prophylactic antimicrobials was suboptimal against most of the microorganisms colonizing the bronchi. The use of broader-spectrum prophylactic antimicrobials would be expected to decrease the rate of infections due to bronchial colonization by pathogenic microorganisms [34].

**Ventilator-induced lung injury**

In recent years, the deleterious effects of mechanical ventilation have been incriminated in the pathogenesis of RC-OCS. One-lung ventilation via selective endotracheal intubation may be particularly harmful. Mechanical ventilation per se may induce a combination of mechanical, hydrostatic, and inflammatory lesions known as ventilator-induced lung injury (VILI) [35]. These lesions have been ascribed to barotrauma, overdistension and, more recently, biotrauma.

One-lung ventilation and the lateral decubitus position are associated with redistribution of both the cardiac output and lung ventilation. Thus, the ventilated lung receives all the cardiac output and mechanical ventilation. The excess
perfusion in the ventilated lung, combined with elevation of the hydrostatic pressure, may damage the lung capillary bed. During re-expansion of the non-ventilated lung, activated mediators of inflammation may be transferred to the other lung, causing ischemia-reperfusion injury [36]. Damage to the endothelium (biotrauma) may cause vasomotor dysregulation in the pulmonary vascular bed via inadequate production of vasoactive compounds (nitric oxide, endothelin, and prostaglandins), thereby diminishing the effectiveness of pulmonary-artery hypoxic vasoconstriction in decreasing shunting. Protective ventilation involving a small tidal volume and positive end-expiratory pressure (PEEP) significantly decreases the occurrence of VILI [37].

The inflammatory response may persist during postoperative mechanical ventilation. Current guidelines emphasize the need to keep postoperative mechanical ventilation as brief as possible and to use fast-track anaesthesia protocols allowing rapid extubation [9, 38]. Intraoperative corticosteroid administration has been suggested as a means of preventing the inflammatory process. However, the results obtained to date are not sufficient to recommend the routine use of this method [39, 40].

**Surgical procedure**

The best approach for oesophagectomy remains debated. There are two main options, transhiatal and transthoracic oesophagectomy, respectively. Transhiatal oesophagectomy (without thoracotomy) causes less respiratory morbidity but is a less radical procedure that produces lower long-term survival rates. Transthoracic oesophagectomy (with a thoracotomy on the right or left side) enables extensive tumour excision but is associated with higher respiratory morbidity rates. In a randomised controlled trial, transthoracic oesophagectomy with extended lymphadenectomy was associated with both a trend toward improved 5-year survival and higher postoperative morbidity and mortality rates, compared to transhiatal oesophagectomy [41]. Subsequent studies confirmed these findings. In 102 consecutive patients treated with transthoracic oesophagectomy, extended lymphadenectomy was independently associated with an increased risk of RC-OCS compared to standard lymphadenectomy [42]. Although mediastinal node dissection undoubtedly improves local disease control, the associated loss of bronchial blood vessels and alterations in lung lymph drainage promote the development of RC-OCS. Thus, the long-term survival advantage must be weighed against the higher risk of postoperative morbidity and mortality. Minimally invasive surgical approaches (laparoscopy and thoracoscopy) were developed in recent years to decrease the surgical trauma and complication rate. Although the preliminary results are promising, they require confirmation by controlled studies [33].

The surgical procedure inevitably causes damage to mediastinal nerves and requires manipulation of the lung parenchyma. Injury to the recurrent laryngeal nerves leads to swallowing impairments and blunting of the cough reflex and may also trigger reflex bronchoconstriction with local mediator release. Oesophageal tumour dissection is a complex and extensive procedure. The long list of possible intraoperative mishaps includes contusions, TNF release by the tumour, section of nerves and/or lymphatics, and inoculation of gastrointestinal bacteria into a sterile site. All these events can contribute to the development of inflammation or infection.

**Postoperative factors**

The postoperative period is crucial for the prevention of RC-OCS. Two interventions are of the utmost importance, namely, appropriate pain management and early respiratory physiotherapy.

**Thoracic epidural analgesia (TEA)**

Several theoretical considerations suggest that thoracic epidural analgesia (TEA) may decrease the complication rate after major surgery. A comprehensive and informative literature review has been published [43]. TEA with local anaesthetics alone or, preferably, in combination with opioids may provide better pain control than parenteral opioid administration, even via a patient-controlled analgesia device. Therefore, TEA should improve coughing and early postoperative mobilization. Furthermore, TEA with local anaesthetics blocks the diaphragmatic function-inhibiting reflexes that occur after abdominal surgery and should therefore minimize the degree of diaphragmatic dysfunction. In theory, TEA promotes adequate peristalsis and may improve gastric tube viability via beneficial effects on the vascular supply. The ability of TEA to improve gastric tube viability and to decrease RC-OCS rates was confirmed recently [44]. A multimodal management strategy with TEA started intraperatively then continued postoperatively on a patient-controlled basis allows early extubation and sitting on the edge of the bed on the first postoperative day [10].

**Non-invasive ventilation**

In theory, NIV can improve ventilatory mechanics and diminish the work of breathing, thereby improving oxygenation and decreasing atelectasis formation. The use of NIV in thoracic surgery patients has expanded in recent years, to good effect [45, 46]. NIV improves PaO$_2$ levels and decreases the alveolo-arterial oxygen gradient. When used for a brief period (1 hour), NIV induces no immediate adverse effects on the lung (increased leakage, increased shunting, or hemodynamic deterioration) or gastrointestinal tract, most notably at the level of the reconstruction. Postoperative NIV produces two beneficial effects. First, it improves oxygenation, thus benefiting the blood supply to the reconstruc-
tion and diminishing the number of complications related to the gastric conduit. Second, NIV exerts early effects on RC-OCS development. Often, bronchial secretion retention or pneumonia can be managed effectively with NIV, which avoids progression to a more serious complication such as ARDS.

Other factors

The intrathoracic gastric or colonic conduit is associated with reflux, which may result in lung micro-aspiration. Recurrent laryngeal nerve palsy is another risk factor for aspiration. For these reasons, many groups [47] advocate the use of a nasogastric tube during the first postoperative days. In the ICU, respiratory physiotherapy should be provided and intravascular fluids should be used sparingly [48]. Blood transfusion has been found to predict death [29] and is involved in the development of postoperative transfusion-related acute lung injury) [49].

- Many factors promote the development of RC-OCS.
- One group of factors is related to the patient (respiratory function impairment before surgery, smoking, poor nutritional status, and induction treatment). Another group depends on the surgical procedure (mechanical ventilation, surgical approach, and prophylactic antimicrobial therapy). Finally, a third group is associated with the postoperative management (thoracic epidural analgesia, postoperative NIV, and fluid management).

Preoperative evaluation of the respiratory risk

The respiratory function evaluation prior to oesophagectomy has no specific features. The investigations are those routinely performed before lung resection surgery, such as lung function testing, bronchoscopy, and a walk test. Cardiac investigations should include an ECG and an echocardiogram. Based on the results and co-morbidities, the patient often requires additional evaluation by dobutamine-echocardiography or even selective coronary arteriography. The nutritional status often deserves assessment, as dysphagia is a common symptom. Nutrition is assessed based on the body mass index, serum protein and albumin levels, 24-hour urinary creatine excretion, serum and urine electrolyte levels, specific vitamin assays, food intake measurements, and other tests. These investigations should be done sufficiently early before surgery to allow for preoperative respiratory preparation and the correction of nutritional deficiencies. Respiratory preparation is crucial to prevent the development of RC-OCS, most notably in patients with reversible ventilation disturbances. Non-reversible disturbances may predict the occurrence of RC-OCS. Thus, the strategy is the same as in lung surgery patients. Lung function tests are also helpful for predicting the patient’s ability to tolerate one-lung ventilation and for setting postoperative blood gas targets, which may govern the management of ventilator weaning. To date, a single study has produced a score for predicting cardiorespiratory complications after oesophagectomy [6]. The score is based on age, performance status on the Eastern Cooperative Oncology Group scale, and the FEV1 value, and the values are classified into risk categories. However, this was a retrospective study in which standardized definitions of RC-OCS were not available [6].

Two investigations may be of considerable importance for predicting RC-OCS: the 6-minute walk test and lung function testing.

Six-minute walk test

The patient is asked to walk as fast as possible for 6 minutes, resting when needed [50]. No encouragement is given, but the patient is told how much time is left. Oxygen can be given to keep the arterial oxygen saturation at 90% (by pulse oximetry, SpO2). At 2-minute intervals, heart rate, blood pressure, and SpO2 are measured. The distance walked is determined at the end of the 6 minutes. In multivariate analyses of data from lung resection patients, a 6-minute walking distance shorter than 200 metres independently predicted postoperative death [51, 52]. The 6-minute walk test is now used routinely in everyday practice. However, its true predictive value in the specific field of oesophageal surgery remains to be established.

Lung function tests

Several findings are widely held to indicate a risk of respiratory complications: a value less than 50% of predicted for FEV1, maximum minute ventilation (MMV), forced expiratory flow at 25%-75% of vital capacity (FEF25-75), and/or the ratio of residual volume over forced vital capacity (RV/FVC); a ratio of FEV1 over vital capacity (VC) less than 70% of predicted; and PaO2 <65 mm Hg and PaCO2 >45 mm Hg with altered lung diffusion capacity. When lung function tests are abnormal, surgery may be postponed to allow for interventions such as smoking cessation, physiotherapy, bronchial preparation via home NIV, bronchodilator therapy and, if appropriate, antibiotic therapy. Repeat testing after these interventions may show noticeable improvements. However, lung function test abnormalities may prompt further investigations, most notably measurement of the transfer factor of the lungs for carbon monoxide (TLCO) or a hyperoxia test to detect shunting. Peak oxygen uptake (VO2 max) has been suggested as an objective index of preoperative cardiopulmonary status before oesophageal sur-
gery. VO_{2\max} values less than 800 mL·min^{-1}·m^{-2} may predict RC-OCS [53].

- Lung function testing and a 6-minute walk test are the first-line investigations for evaluating patients prior to oesophagectomy.
- The clinical strategy is identical to the preoperative management before lung resection surgery.
- The presence of non-reversible respiratory abnormalities may be the most sensitive predictor of RC-OCS.
- In many patients, surgery must be postponed to allow for interventions aimed at improving respiratory function (e.g., smoking cessation, non-invasive ventilation, and bronchodilator therapy).

Influence of postoperative respiratory complications on long-term survival

RC-OCS have been recognized in recent years as directly influencing not only postoperative mortality, but also long-term survival. In a recent study, the multivariate analysis identified postoperative pneumonia as independently affecting long-term survival [54]. Thus, 5-year survival was 26% in the group with pneumonia and 53% in the group without pneumonia. A similar effect of acute respiratory complications has been reported: median survival was 2.1 months in the patients with RC-OCS compared to more than 16 months in the other patients [28]. Nevertheless, these findings should be assessed with caution, as they reflect multiple factors and artefacts. First, the statistical method should be considered: patients who die postoperatively must be excluded from the survival curves to avoid the bias introduced by fatal postoperative complications. Second, disease-free survival may be a more relevant oncological outcome than overall survival. Among 138 patients managed at our centre, after excluding the patients who died within 90 days after surgery, the 3-year disease-free survival rate was 35% in the group with RC-OCS and 54% in the other group (unpublished data). The impact of RC-OCS on recurrences is probably ascribable to two factors: RC-OCS generate impairments in cellular immunity, which promote cancer cell dissemination; and they lead to delays of several months in the initiation of adjuvant therapy, thereby promoting recurrences. Further work is needed to assess the impact on long-term survival, which underscores the importance of treating RC-OCS early on not only to diminish postoperative mortality, but also to increase survival and to decrease recurrence rates.

Conclusion

The postoperative management of oesophagectomy patients requires the involvement of a multidisciplinary, specialized, and well-coordinated team. Case volume is inversely correlated with operative mortality. Clearly, oesophagectomy should be reserved for carefully selected patients managed at reference centres. The management and mechanisms of complications of oesophagectomy are identical to those in lung cancer patients.

Specific management strategies and improved understanding of the pathophysiology of RC-OCS have decreased the associated postoperative mortality rate. However, effective prevention is still far beyond reach, and the RC-OCS incidence rate has unfortunately remained unchanged for the last 20 years. The main effect of advances in surgical and anaesthesiological techniques has been to decrease respiratory complications caused by surgery-induced structural damage. In the future, data from the various research projects investigating the pathophysiology of RC-OCSs will provide major improvements, most notably in the field of microbiology.

Preoperative respiratory preparation involving both the pulmonologist and the surgeon remains crucial for RC-OCS prevention. Several weeks before surgery, a number of interventions are mandatory, including smoking cessation, individually tailored respiratory physiotherapy, and training in the use of ventilators. During and after surgery, patients must receive standardized management based on a number of preventive measures such as routine use of lung-protective ventilation strategies, optimal fluid management conducted under close monitoring, minimization of the time on ventilatory assistance (early extubation and fast-track recovery program), and optimization of ventilation mechanics (TEA, intensive physiotherapy, and early mobilization). In all likelihood, the combination of all these measures will prove the key to decreasing the RC-OCS rate.

KEY POINTS

- Among patients treated with oesophagectomy, over 30% experience postoperative respiratory complications (bronchial secretion retention, nosocomial pneumonia, or acute respiratory distress syndrome [ARDS]), of which 80% develop within the first 5 days.
- In high-volume centres, the operative mortality rate is 5% to 10% and 5-year survival is nearly 35%.
- Complications related exclusively to respiratory factors range from bronchial secretion retention to ARDS.
- Complications caused by structural damage during surgery consist of pleural effusion, anastomotic leaks, haemothorax, and chylothorax.
• Risk factors fall into three groups: patient-related factors (age, immune deficiency, malnutrition, baseline respiratory function impairments, and concomitant treatments), intraoperative factors (type of anesthesia with the impact on ventilation, prophylactic antimicrobials, ventilation modalities, and surgical procedure), and postoperative factors (analgesia modalities, ventilation modalities, and digestive fluid reflux).
• The prevention of RC-OCSs rests on optimal respiratory preparation before surgery.
• The preoperative workup is the same as for lung resection surgery: lung function testing, bronchoscopy, and walk test.
• RC-OCS directly influence both postoperative mortality and long-term survival.

References


