

Society for Translational Medicine Expert Consensus on the prevention and treatment of postoperative pulmonary infection in esophageal cancer patients

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Esophageal cancer is ranked as the malignant tumor with the 6th highest morbidity and mortality rate worldwide. Chinese people are prone to develop esophageal cancer, and the number of new cases that occur every year account for more than half of the esophageal cancer patients worldwide (1,2). Although reports have confirmed the effectiveness of chemoradiotherapy for esophageal cancer, esophageal resection remains the primary means of treatment. Anastomotic leaks and pulmonary complications are the most common postoperative complications of esophageal cancer and carcinoma of the gastric cardia. Pulmonary complications have become more noticeable (3) as the incidence of postoperative anastomotic fistula (8–15%) has decreased due to the improvement of surgical techniques, the use of disposable staplers, and the continuous improvement of postoperative nutritional support. Cervical and upper thoracic esophageal cancer are associated with a higher risk for postoperative pulmonary infection.

The pathophysiologic mechanisms that lead to pulmonary infection after esophageal cancer surgery include alveolar collapse, pulmonary edema, weakened pulmonary defense mechanisms, and poor ventilation (4). Perioperative risk factors associated with postoperative pulmonary infection include the existence of pulmonary inflammation and suboptimal control of infection before surgery for patients with chronic bronchitis, chronic cardiac insufficiency, age [≥ 80 years (5)], a long disease course, obesity (6), smoking (7), excessive drinking, diabetes, malnutrition (7), chronic obstructive pulmonary disease (COPD) (8), preoperative chemotherapy (9), intraoperative use of single lung ventilation, and large intraoperative blood loss (10). In order to reduce postoperative pulmonary complications during esophageal cancer surgery, protective strategies should include an accurate assessment of the patient's preoperative pulmonary function (11); a good understanding of the effect of applying respiratory irritant drugs during anesthesia and the effects of anesthesia on the respiratory tract; attention to reduce physical damage to lung tissue while using double-lumen tracheal intubation; and the application of active measures after surgery, such as, prophylactic antibiotics, pulmonary toilet and nutritional support. Recurrent laryngeal nerve (RLN) injury continues to play a critical role in the development of postoperative pulmonary infection during cervical and upper thoracic esophageal carcinoma resection, with an incidence rate of approximately 1.2–15.0% (12). This review paper will address important aspects of diagnosis, prevention and treatment of postoperative pulmonary infections in esophageal cancer patients.

Diagnosis

The clinical diagnostic basis for postoperative pulmonary infection in esophageal carcinoma patients is the same diagnostic criteria used for “hospital acquired bronchial-pulmonary infection” which includes the presence of obvious clinical symptoms such as the onset of cough, sputum, or sputum trait changes at 48 h after admission and meeting one of the following criteria:

- (I) Persistent fever (body temperature >38 °C) for more than 2 days, new pulmonary rales, or the occurrence of new inflammatory lesions on chest X-ray examination.
- (II) Isolation of the same pathogen in two sputum samples and smear microscopy showing <10 squamous cells/low magnification field of view, leucocyte quantity >25 /low magnification field of view, or the ratio of these two $<1:25$. If possible, the samples should be sent to the laboratory for sputum washing and quantitative culture within 10 minutes of collection. The isolated pathogen concentration should be $>10^7$ CFU/mL.
- (III) Positive blood culture or pathogen isolation by thoracentesis of a parapneumonic effusion.
- (IV) Pathogen isolation from any of the following methods which are generally considered free of contamination: $\geq 10^5$ CFU/mL of pathogenic bacteria isolated from lower respiratory tract secretions collected through fiberoptic, bronchoscopy aspiration, thyrocricocentesis attractors (TTA) or a protected specimen brush (PSB). The bacterial concentration must be higher than 10^3 CFU/mL for COPD patients.
- (V) Detection of specific pathogens (including *Legionella spp.*) in respiratory secretions, serum and other body fluids using immunological methods (i.e., immunofluorescence assay) or histopathological analysis.

Although many scholars have attempted to establish a scoring system for admission to the intensive care unit (ICU) after esophageal cancer surgery, specific criteria for ICU admission has not been widely accepted (13–16). Risk factors associated with postoperative ICU admission include the presence of preoperative COPD, higher American Society of Anesthesiologist (ASA) scores, large intraoperative blood transfusion, postoperative neurological dysfunction (which might be closely associated with the occurrence of postoperative sepsis), and cardiac arrhythmias (17,18).

Prevention

Preoperative measures

- (I) Smoking cessation: smoking is a risk factor for the occurrence of postoperative pulmonary infection. Some researchers have demonstrated that quitting smoking 3 months before esophageal cancer surgery can effectively reduce the rate of postoperative pulmonary complications (19).
- (II) Chest physiotherapy: cough, expectoration, deep breathing (orthopnea breathing or spine abdominal breathing 3 min/twice/day), and pursed lip breathing exercises can reduce the incidence of postoperative pulmonary complications (by 8%) (20).
- (III) Five minutes of teeth and tongue cleaning should be performed at least once per day after surgery.
- (IV) Methyl prednisolone prior to surgery can reduce esophageal cancer overall postoperative complications and pulmonary complications. In 2010, a meta-analysis of 6 randomized control trials showed that preoperative use of a single dose of methyl prednisolone reduced the occurrence rate of pulmonary complications from 28.6% to 15.4% (RR =0.66) (21).
- (V) Alcohol cessation: similar to smoking, drinking has been proven in worldwide studies to be a risk factor for increased postoperative complications. Therefore, quitting drinking before the operation can have an important effect on reducing the rate of postoperative complications.
- (VI) Preoperative chemoradiotherapy: results from multiple meta-analyses worldwide have demonstrated (22) that preoperative chemoradiotherapy improves the prognosis of patients compared to surgery alone. Currently, many internationally renowned academic organizations or institutions, such as the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Organization for Research on Treatment of Cancer (EORTC), include preoperative chemoradiotherapy in combination with surgical treatment in their treatment guidelines for esophageal cancer as the standard of care. Targeting the high incidence of esophageal squamous cell carcinoma in China, the Chinese Anti-Cancer Association Professional Committee of Esophageal Cancer developed the “Chinese esophageal cancer standardized

treatment guidelines” in 2011, which suggested that preoperative chemoradiotherapy could be used for thoracic esophageal carcinoma patients (especially squamous cell carcinoma patients with a preoperative clinical staging of T₃N₀M₀, T₁₋₂ associated with lymph node metastasis, and T₃₋₄ associated with or without lymph node metastasis); however, the dose should not be too high and should be controlled within the 50 Gy range.

- (VII) Nutritional support: malnutrition in patients could cause respiratory muscle weakness, leading to an increased incidence of postoperative respiratory complications, such as pulmonary infection (23). Correcting anemia and hypoproteinemia (serum albumin should be adjusted to approximately 25–30 g/L) prevented left ventricular failure.
- (VIII) Exclusion of patient with poor pulmonary function: The risk of postoperative cardiopulmonary complications is high with a preoperative ratio forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) <65% of predicted. DeMeester and Barlow (24) suggested that patients with a FEV₁ <1 L should not undergo esophagectomy.
- (IX) Glucose control: some studies suggest that diabetic patients with a fasting plasma glucose of 7 mmol/L before surgery had lower incidence of postoperative pulmonary infection (25).

Intraoperative measures

- (I) Select an incision with less postoperative pain, stomach as preferred esophageal replacement conduit.
- (II) Shorten the anesthesia and surgery time: the incidence of pneumonia in patients with surgery times <2 h and >3–4 h is 8% and 40%, respectively.
- (III) Use anesthesia methods and drugs with little lung function impairment to maintain a slightly large tidal volume ventilation (8–10 mL/kg). Recently, Downs *et al.* found that an “open-lung” ventilatory technique maintained oxygenation and prevented atelectasis (26).
- (IV) Routinely use a nasoduodenal feeding tube or a jejunostomy feeding tube for enteral nutrition. The feeding tube or fistula catheter can be removed once the patient’s diet is close to normal.
- (V) Attempt anastomosis below the aortic arch: Banki

et al. (27) suggested that anastomosis above the aortic arch caused more severe pulmonary contusion than anastomosis below the aortic arch and a more pronounced reduction or damage to the alveolar surfactant. Damage to the bronchial branch of the vagus nerve and branch of the lung can decrease the excitability of the cough reflex; therefore, there is higher prevalence of pulmonary infection after anastomosis above the aortic arch.

- (VI) Avoid RLN injury: the RLN is particularly vulnerable to injury during tumor and lymph node dissection in the cervical and upper thoracic region. When dissecting the esophagus above the left RLN from the left vagus nerve, dissection should be made close to the esophagus using blunt dissection.

Postoperative measures

- (I) Position by nursing: if possible, try to adopt a semi-recumbent position 24 h after surgery; this position can benefit breathing exercises and encourage patients to cough and expectorate.
- (II) Adequate analgesia: appropriate postoperative epidural analgesia can increase chest wall motion, reduce the respiratory rate, and increase tidal volume, leading to increased alveolar ventilation.
- (III) Guided breathing: postoperative pulmonary complications in esophageal cancer patients often occur 24–72 h post-surgery; therefore, breathing guidance should be provided for patients who are conscious after anesthesia. The patients should take 10–20 deep breaths every 2 h. Strengthen abdominal breathing in the supine position until the chest drainage tube is removed 48–72 h post-surgery.
- (IV) Assisted expectoration: press the trachea of the patients above the sternal incisura with the index and middle fingers to stimulate coughing up of sputum.
- (V) Respiratory humidifying: a high-frequency aerosol inhaler should be used 2 to 3 times a day for 1 week.
- (VI) Timely suctioning: use a nasal suction catheter for patients with a large quantity of sputum, viscous sputum, and powerless expectoration. If necessary, use a fiber bronchoscope for suctioning.

Treatment

- (I) Assisted expectoration: postoperative pulmonary

edema, increased sputum production, ineffective cough and expectoration are important manifestations in most esophageal cancer patients with pulmonary infections. Assisting patients with effective expectoration is one of the main measures to treat lung infections. Patients should be encouraged to drink water. Intravenous fluids are given to increase the total body water. However, for patients with some organic heart diseases, such as coronary heart disease and hypertension, the infusion rate should be reduced based on observations of changes in the heart rate and blood pressure; an attempt should be made to control the 24 h intake to approximately 2,500 mL. Continuous medical ultrasonic nebulizer inhalation of an aerosolized solution containing an antibiotic and an expectorant agent (5 mL of saline, 2,000 U of chymotrypsin, 15 mg of Mucosolvan, and 80,000 U of gentamicin) through a mask can often achieve good airway humidification effects and improve the patient's hypoxic condition. A vibration expectoration instrument can be used to assist expectoration, which can reduce the chance of complications such as atelectasis and accelerate the healing and rehabilitation of the patient, thereby reducing the number of days in the hospital. For patients with endotracheal intubation or a tracheostomy, sterile saline can be injected through the endotracheal tube or tracheostomy tube in a sequential manner for suctioning as follows: the patient is placed in left lateral decubitus position; after suction, 2–10 mL of sterile saline is injected inside the cannula to allow the saline flow into the left bronchus. Then, the patient is turned over into the right lateral decubitus position so that suction can better aspirate secretions from the left bronchus. The following procedures can be performed to allow most patients to better aspirate sputum depending on the sputum humidifying conditions: suction, injection of moisture, standing up, shooting back, and suction approximately once every 1–2 h. When patients have a large quantity of sputum and ineffective coughing up, shallow and cramped breathing, and a blood gas analysis showing a more obvious respiratory failure occurrence, endotracheal intubation and tracheal suctioning with or without supplementation

by positive pressure ventilation are the only effective measures. The sooner these procedures are performed, the better the effect. Because pulmonary edema is a serious lung infection, the pressure and tidal volume of the ventilator should be appropriately controlled to prevent alveolar rupture. Fiber bronchoscope suctioning and bronchoalveolar lavage treatment can accurately collect secretions from the lesion site for bacteriological examination and drug sensitivity testing and provide evidence for the performance of postural drainage in patients. These techniques can also improve the respiratory tract obstruction caused by the sputum, atelectasis, the rapid increase in blood oxygen, and the decrease in the carbon dioxide partial pressure. The effect is especially improved if used in the early stage, which can cause the release of early airway obstruction and improve ventilation. For patients with no cough reflex, bronchoalveolar lavage is not recommended to avoid fluid retention in the bronchi and alveoli, which can lead to serious consequences such as hypoxia and asphyxia.

- (II) Postoperative analgesia: the pain caused by the thoracic wall incision and drainage tube can make patients fear the pain and reduce their depth of breathing, leading to a refusal to cough or a weak cough that impairs the ipsilateral lung ventilation function and does not allow sputum to be effectively discharged. Therefore, it is also necessary to prophylactically administer analgesic pain medication to fully relieve the pain. Based on the degree and pattern of the pain and the time of the first effective pain relief, timely administration of non-opioid drugs to maintain the drug concentration in the blood will keep the pain stimulus controlled below the pain threshold as much as possible. This procedure will allow the patients to tolerate the pain caused by the coughing and respiratory activity and will enable them to initiate the deep breathing exercise and coughing expectoration. Thoracic epidural analgesia (TEA) is usually considered the gold standard technique of choice for post-thoracotomy pain relief. TEA provided better analgesia than conventional analgesia techniques in post-thoracotomy pain. However, there are limitations for this method which is not suitable

for all patients and is associated with many risks. Continuous intercostal nerve block (IB) was shown to provide adequate pain control following thoracotomy, but offers potential opportunity for introducing infection. Overall, effective management of acute pain following either thoracotomy/thoracoscopy is needed and may prevent these complications and reduce the likelihood of developing chronic pain (28).

- (III) Application of antibiotics: Application of effective antibiotic treatment is undoubtedly one of the most effective ways to control pulmonary infection. The selection of antibiotics should fully take into account the presence of Gram-negative *Escherichia coli*, *Staphylococcus aureus*, and/or the possibility of an anaerobic infection. Unless there is support from bacterial culture and drug sensitivity tests, broad-spectrum antibiotics should not be started to avoid drug-resistant strains and a flora imbalance. It is better to screen the antibiotics and regularly review their administration in accordance with the sputum or blood culture results because patients often have two or more bacterial infections and these infections vary as the disease and treatment progress. When using antibiotics for prophylactic purposes, narrow-spectrum antibiotics should be used. After pulmonary infection occurs, gastrointestinal surgery should be considered before the drug sensitivity result is available. The possibility of a Gram-negative and anaerobic bacterial infection is considerable. Thus, reasonable use should be made of combined antibiotics. The hospital bacteria trends should be known and the antibiotic resistance of the bacteria should be considered before applying antibiotics. If antibiotics need to be used for a long time, doctors have to pay attention to the possible occurrence of a superinfection.
- (IV) Nutritional support: esophageal cancer patients usually have difficulty eating and present with malnutrition prior to the surgery. These patients have fewer nutritional reserves and cannot eat for a long time after the surgery. They are prone to a cough and weakness caused by malnutrition as well as compromised immune functions after the surgery. This situation is more obvious in elderly patients, which is one important reason

for the increased postoperative incidence of complications and mortality. Studies have shown that the use of enteral nutrition after surgery can effectively reduce the incidence of postoperative pulmonary infections (27,29). Earlier use is more effective at reducing the postoperative pulmonary infection incidence (30,31). Esophageal cancer postoperative enteral nutrition and parenteral nutrition can effectively improve the nutritional status in terms of recovery nutrition indicators. Compared to parenteral nutrition, enteral nutrition support is safe and effective and can greatly reduce the cost of nutrition. More importantly, enteral nutrition support can maintain a relatively normal gastrointestinal physiological state, reduce bacterial translocation, improve patient immunity, and promote recovery of gastrointestinal functions. Esophageal cancer postoperative enteral nutrition and parenteral nutrition have their own indications as well as advantages and disadvantages. Their applications should cooperate and complement each other. In principle, enteral nutrition should be preferentially used for patients with a normal digestive tract. Parenteral nutrition supplements should be administered when enteral nutrition is insufficient. Never place undue emphasis on the advantages and disadvantages of one certain type of nutrition and the use of one single nutrition approach; this approach is particularly important in patients with severe pulmonary infection and fever resulting in energy consumption increases. When nasal feeding through the gastric tube or the nasal intestinal tract, a continuous feeding rate should be used that ensures that the stomach contents are less than 30% (by volume) of the residual stomach to avoid excessive expansion of the stomach, which can cause an overflow of food and lead to aspiration (32).

- (V) Supported cardiac function: most elderly patients have insufficient heart and lung functions, poor reserves, and other conditions. After surgery, coronary dilatation drugs should be routinely used to prevent postoperative myocardial ischemia; cardiac and diuretic drugs should be selectively used to improve heart functions. The principles of assisted cardiac function primarily increase myocardial contractility, reduce the cardiac

preload and afterload, provide blood pressure control based on the preoperative situation, and allow reasonable transfusion. Due to decreased cardiovascular system function in elderly patients, the positive infusion volume and rate should be strictly controlled to avoid inducing heart failure. Postoperatively, pain, anxiety, endogenous catecholamine release, and increased myocardial stress, may lead to arrhythmia (33). Appropriate postoperative analgesia and sedation may reduce the incidence of arrhythmias.

- (VI) Prevention of aspiration pneumonia: saliva secretion is reduced during the esophageal cancer postoperative fasting period. Additionally, oropharyngeal bacteria can easily multiply because it is often inconvenient to perform brushing, mouthwash, and other oral hygiene measures (34). Barkov *et al.* (35) reported that gastric juice-induced aspiration pneumonia was most common in esophageal cancer after surgery. For gastric juice-induced aspiration pneumonia, a tracheal incision should be performed in a timely manner to allow repeated suction and a ventilator should be used to maintain breathing. Anti-inflammatory and hormonal drugs and other treatments should be actively administered. The fiberoptic bronchoscope should be regularly used for endotracheal suctioning, and saline, gentamicin, and chymotrypsin should be used for bronchial flushing.
- (VII) Ensuring good operative side lung reexpansion: postoperative patency of the continuous gastrointestinal decompression plays an important role not only in the prevention of anastomotic leakage but also in reducing thoracic gastric oppression of the lung and aspiration pneumonia. Studies showed that arch anastomosis had a more significant effect on postoperative respiratory functions due to the larger position occupied by the stomach in the chest cavity than arch anastomosis. If poor drainage of the gastric tube occurs after surgery, the thoracic gastric dilatation increases pulmonary collapse, which very easily leads to the occurrence of postoperative pulmonary infection and respiratory failure. Ensuring continuous and effective thoracic drainage, promoting lung recruitment, and avoiding a hemothorax are important steps in the treatment of pulmonary infection to reduce

secondary empyema.

- (VIII) Elderly patients usually have pancreatic islet dysfunction or other metabolic diseases. Blood sugar should be tested at the same time nutrition support is provided. A continuous infusion of insulin with a micro-pump should be routinely used to maintain blood sugar in the 6–10 mmol/L range. Studies showed that the occurrence rates of postoperative pulmonary infection, anastomotic leaks, and other complications in esophageal cancer patients were closely associated with hyperbilirubinemia (36). Shimada *et al.* reported that steroid treatment effectively reduced the postoperative hyperbilirubinemia occurrence rate from 26% to 5% (37).

In summary, the treatment for postoperative severe pulmonary infection in esophageal cancer patients should not solely rely on anti-infection treatment but should also include early comprehensive treatment measures, such as assisted expectoration, enhanced nutrition support, improvement of cardiac function, prevention of aspiration pneumonia, ensured lung recruitment, and prevention of excessive inflammation, which can significantly improve the cure rate in patients.

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Footnote

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