



Enhanced recovery after surgery pathway in esophagectomy in a high volume center: clinical keys to early leak diagnosis after esophagectomy

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Abstract: At present, standard treatment for potentially curable esophageal cancer includes neoadjuvant chemoradiotherapy followed by esophagectomy with lymphadenectomy. One of the complications with potentially serious consequences after esophagectomy is an anastomotic leakage. This complication is associated with prolonged hospital stay, morbidity, and mortality. In the postoperative period it can be challenging to recognize this complication and make a differentiation from other complications, such as pneumonia. Early recognition is a prerequisite for prompt treatment, which is known to lead to improved results. Nowadays, most centers performing esophagectomies use a standardized enhanced recovery after surgery (ERAS) program to treat patients peri-operatively. These programs should also include strategies to early detect and treat anastomotic leakage. This article describes the ERAS program developed at the upper GI unit of the University Medical Centre Utrecht, the Netherlands. It explores the various aspects of such a pathway, such as postoperative monitoring, nasogastric tube management, feeding protocols, early warning signs and diagnostics to be used in case of suspicion of a complication. In addition, the ERAS program is clarified with available relevant literature on different topics of the perioperative management for esophagectomy patients. The main focus of this article is the early recognition and detection of anastomotic leakage, which enables aggressive treatment.

Keywords: Esophagectomy; anastomotic leakage; postoperative complications

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Introduction

Esophageal cancer is an aggressive cancer which is associated with a poor survival. The standard of care for patients with locally advanced esophageal cancer is neo-adjuvant chemo(radio)therapy followed by radical esophagectomy with lymphadenectomy (1). Anastomotic leakage remains a frequently encountered complication with reported frequency ranging from 11.4% up to 30% (2,3). Because of the potentially harmful effect of extravasation of gastro-intestinal contents, this is a feared complication after

esophageal surgery. Early detection of anastomotic leakage is crucial, as delayed start of treatment, which for example can result in mediastinitis and empyema, is associated with prolonged hospital stay, morbidity, and mortality (4,5).

A standardized postoperative recovery program can be helpful in early detection of complications and thereby improving the outcome after esophagectomy. Enhanced recovery after surgery (ERAS) pathways are designed to optimize perioperative care by a multimodal approach to the surgical patient (6). However, the optimal management

strategies for detection of anastomotic leakages after esophagectomy are unclear (7,8). This study aims to review the available literature on the postoperative management after an esophagectomy including strategies to early recognize and detect anastomotic leakage and reflect on this from our experience.

Esophagectomy ERAS pathway UMCU

Esophagectomy

In our institute we routinely perform a fully robot-assisted minimally invasive esophagectomy (RAMIE). This includes a two-field lymphadenectomy (including mediastinal stations 2–9), gastric conduit reconstruction, and an intrathoracic anastomosis (Ivor Lewis) or a cervical anastomosis (McKeown). In our hospital, we perform a three-stage esophagectomy with a cervical anastomoses if indicated, for example in patients with an upper esophageal tumor, a Barrett's segment extending into the upper esophagus, neoadjuvant radiation of the upper esophagus, or if a cervical lymph node dissection is indicated. Otherwise, for example in patients with a lower esophageal tumor we perform a two-stage esophagectomy with an intrathoracic anastomosis. The technical steps of RAMIE procedure were described in detail in previous publications (9). During the postoperative period patients will follow a standardized ERAS protocol.

Postoperative monitoring

During the postoperative time, the patient will be closely monitored to look for signs of complications. This close monitoring will first take place at the intensive care unit (day 0 postoperative), medium care (day 1 postoperative), and the regular upper GI surgical ward (day 2 postoperative). Specific manifestations include swelling and erythema of the cervical wound, in case of a cervical anastomosis, or change of the chest drain output, in case of an intra-thoracic anastomosis. Also tachycardia, new-onset atrial fibrillation (AF) and fever are alarm symptoms for possible complications (10). Other signs of sepsis related to mediastinitis such as subcutaneous emphysema, thoracic pain, pneumothorax, respiratory failure, or pleural effusion should warrant active further investigation.

During the first 3 days postoperatively laboratory diagnostics will be performed routinely. This will consist of infection parameters such as leucocyte count and C-reactive

protein (CRP) as well as electrolytes, glucose, and hemoglobin. If alarm symptoms are present immediate start of supportive care by means of IV fluids, antibiotics, oxygen, and transfer to a high care unit should be considered, depending on the clinical status of the patient. A computed tomography (CT) of both chest and abdomen will be performed to rule out an anastomotic leakage or other complications. If the CT scan is inconclusive an endoscopic examination will be performed to visualize the anastomosis as well as the gastric conduit.

Decompressive nasogastric tube

After esophagectomy, in which a gastric conduit is used to restore gastro-intestinal continuity, a decompressive nasogastric tube is often used. The routinely use of a decompressive nasogastric tube postoperatively is debatable. A meta-analysis showed that perioperative or early removal of the nasogastric tube did not result in different rate of postoperative complications such as anastomotic leakage (11). Therefore, several units omitted the routine use of a nasogastric tube. However, in our institution we routinely use a nasogastric tube to reduce fluid accumulation and gastric distension. We use a 14 or 16 French nasogastric tube which is inserted shortly after start of surgery. During creation of the anastomoses the nasogastric tube is positioned at about 10 centimeters below the anastomoses and attached with a Bridle (Applied Medical Technology, Ohio, USA) nasal tube retaining system. This nasogastric tube will be *in situ* till day 4 postoperatively. We routinely perform a contrast swallow examination at day 4 postoperatively. This study examines both the swallow function of the patient, considering potential laryngeal recurrent nerve damage, and observes the emptying of the gastric tube, regarding potential delayed gastric emptying (*Figure 1*). To accurately observe the swallow function of the patient this study is performed under supervision of a speech therapist. The contrast swallow study is not primary performed to diagnose or rule out an anastomotic leakage.

Average day to start oral feeding

After removal of the nasogastric tube patient will start oral intake containing water and clear fluids at day 4 postoperatively. The next day, a soft and pureed diet will be administered, which is maintained till the patient's first visit to the outpatient clinic postoperatively, which is routinely

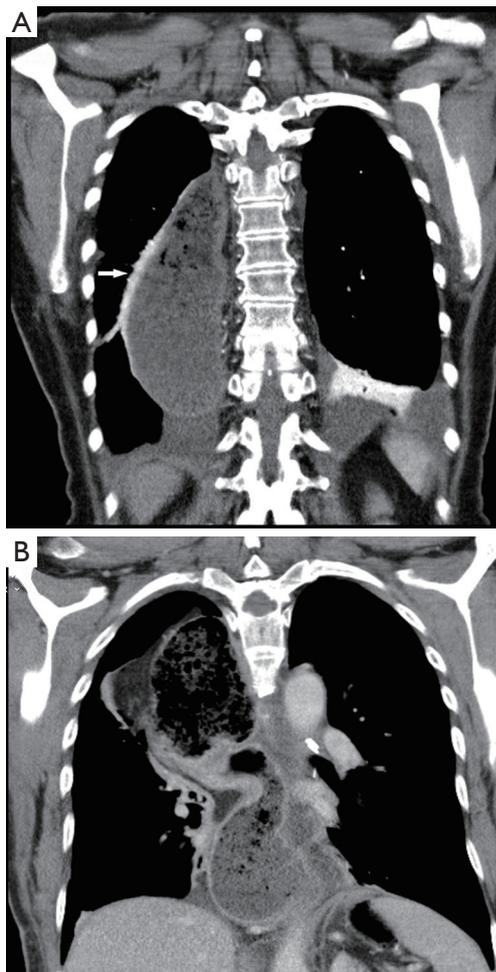


Figure 1 A CT scan conducted 2 days postoperative showing dilatation of the gastric tube with states of fluid in the gastric tube, as sign of delayed gastric emptying (arrow). (A) CT-scan shows dilated gastric tube after esophagectomy. (B) CT scan shows dilated gastric tube after esophagectomy. CT, computed tomography.

planned at about 14 days after surgery.

In our institute we routinely place a percutaneous jejunostomy at the end of the abdominal phase of the esophagectomy. Main goal of this feeding tube is to realize adequate nutritional intake during the period a patient needs to get used to the new feeding regimen after the esophagectomy. Earlier, it was demonstrated that following an esophagectomy about 40% of the patients required nutritional intervention by nasojejunal tube or total parenteral nutrition if oral intake was started early postoperative and a jejunostomy was omitted during the esophagectomy (12). However, several upper GI units start oral feeding directly

after an esophagectomy (13). Recently, a randomized controlled NUTRIENT-2 trial comparing direct start of oral feeding after an esophagectomy with a nil-by-mouth regimen for 5 days postoperative revealed that direct oral feeding after esophagectomy did not increase incidence of complications such as anastomotic leakage and pneumonia (14). In line with this, several upper GI units omit the use of a percutaneous jejunostomy as they start oral intake immediately postoperatively. However, the debate whether a percutaneous feeding jejunostomy is necessary is still ongoing. A recent study which evaluated the use of an jejunostomy in patients undergoing esophagectomy demonstrated that omitting percutaneous feeding jejunostomy placement was associated with prolonged hospital stay, higher in-hospital mortality and 30-day mortality (15). Another argument for tube placement is the expected weight loss that patients will suffer in the months following esophagectomy (16). However, the routine use of a percutaneous jejunostomy is related with serious complications. For example, the earlier mentioned Nutrient 2 trial for example showed in 7.5% of the patients a jejunostomy related complication. A retrospective study from our unit showed jejunostomy-related problems like luxation, occlusion, or reoperation in 31% of the patients (16).

Depending on the recovery of the patient we tend to remove the jejunostomy at about 8 weeks postoperatively. However, if an anastomotic leakage has been diagnosed, patient will be nil by mouth for an undefined period. During this period the patient will receive adequate nutritional intake administered through the jejunostomy, under the careful supervision of a dietician.

Early recognition of complications

Clinical symptoms

Early diagnose and treatment of postoperative complications is essential and may improve patient survival. During the postoperative time patients will be closely monitored to look for signs of complications. Specific manifestations of an anastomotic leak include a change of the chest drain output or swelling and erythema of the cervical wound. This immediately warrants both treatment, for example opening of the cervical wound or antibiotic treatment, and CT of both chest and abdomen to visualize possible thoracic involvement. If an anastomotic leakage occurs following a transthoracic esophagectomy with a cervical anastomoses, 60% of these patients developed an intrathoracic manifestation while in about 40% of the

patients the leakage was confined to the neck (7). Therefore, awareness of possible intrathoracic spread of leakage of a cervical anastomoses is important for early recognition.

New-onset AF, fever, or extensive pain are alarm symptoms which warrant further examination. For example, new-onset AF is frequently observed after esophagectomy and may predict postoperative complications (17). Recently, it was demonstrated that new-onset AF is highly associated with post-operative complications like pneumonia and anastomotic leakage (10). Since AF seldomly occurs without other postoperative complications, further investigation (e.g., laboratory diagnostics, chest X-ray or CT scan) to evaluate patients with new-onset AF is recommended.

Laboratory diagnostics

Routine laboratory tests, in particular CRP and leukocytes, are used to monitor patients postoperatively and to screen for postoperative complications, such as anastomotic leakage. CRP is an acute-phase protein that is synthesized in hepatocytes in response to pro-inflammatory cytokines (18). CRP is secreted into the blood in response to inflammation and infection. Postoperative CRP is a predictor for postoperative complications, such as anastomotic leak, after esophagectomy (19). Several studies determined the relation between postoperative CRP increase and postoperative complications. For example, an elevated CRP (>177 mg/L) at day 2 postoperatively was shown to have a sensitivity of 0.9 and a specificity of 0.95 for anastomotic leakage after radical gastrectomy with esophageal-jejunum reconstruction (20). More recently, in patients who underwent a thoraco-abdominal esophagectomy a CRP increase on the second postoperative day above 200 mg/L was an independent positive predictor for postoperative complications (21). In conclusion, routine laboratory tests postoperatively have diagnostic value for anastomotic leakage. Early elevated pro-inflammatory markers warrants careful physical examination and further diagnostics test to detect possible complications after esophagectomy. However, results from randomized controlled trials are needed to exactly determine the role of inflammatory markers on outcome and prognosis. New markers, such as procalcitonin, septicity and others are promising and warrant further evaluation (22).

Radiology

A CT scan is often performed to diagnose a postoperative

anastomotic leakage, since it is non-invasive and safe to use in critically ill patients. In addition, it also aids in the detection of other associated findings such as pulmonary complications. Several studies have evaluated the efficacy of CT scanning for the detection of anastomotic leakage after esophagectomy, for example compared with contrast swallow examination, and showed better results with a CT scan for diagnosing an anastomotic leakage (23,24). Recently, our study group demonstrated that the presence of mediastinal fluid, mediastinal air, esophagogastric wall discontinuity and a fistula on a postoperative CT are strongly associated with anastomotic leakage after esophagectomy in patients with a clinical suspicion of anastomotic leakage (*Figure 2*) (25). In addition, a CT-based prediction score was developed for the detection of anastomotic leakage after esophagectomy. However, it can be difficult to confirm the significance of small pockets of fluid and air located in the mediastinum when CT scanning is performed in the first week postoperative. If the results of the CT are doubtful, an endoscopy for further analysis is recommended.

Contrast swallow examination

Worldwide, a water-soluble contrast swallow is routinely carried out around day 4 to 7 postoperatively to detect anastomotic leakage. However, limitation of routine contrast swallow in the detection of anastomotic leakage is the poor sensitivity. Our group demonstrated that a contrast swallow performed around day 7 postoperative had low sensitivity and low predictive value in patients with a cervical anastomoses (26). In addition, at this time-point over 50% of the patients with an anastomotic leakage already had clinically presentation, so before the contrast swallow examination was routinely planned. This is in line with other studies which also showed a poor sensitivity of contrast swallow examination to detect anastomotic leakage (27,28). A prospective trial that compared the accuracy of CT with oral contrast, endoscopy and contrast swallow for the detection of anastomotic leakage following esophagogastric surgery, concluded that a CT scan is more reliable compared with a contrast swallow to detect an anastomotic leak after an esophagectomy (24).

Endoscopy

Historically, surgeons have been reluctant to utilize endoscopic examination early after esophagectomy as this invasive procedure may damage the anastomosis.

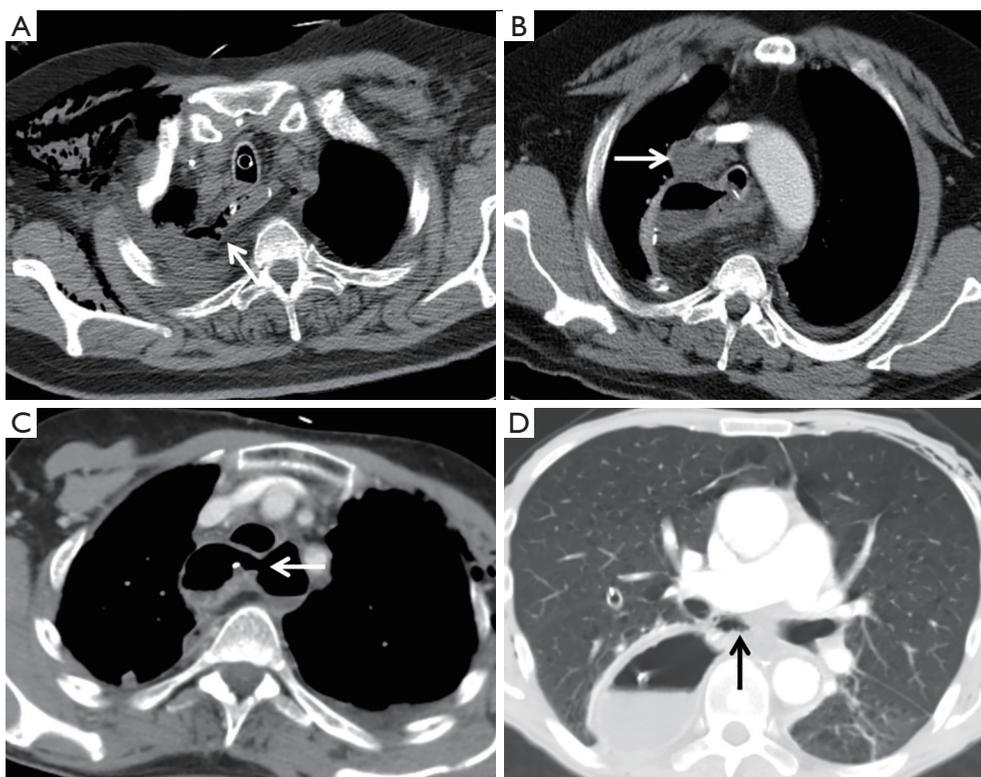


Figure 2 Examples of CT findings associated with manifestation of anastomotic leakage after esophagectomy. (A) CT-scan shows a fistula between the gastric tube and the right pleural cavity (arrow). (B) CT-scan shows a fluid collection in the mediastinum (arrow). (C) CT-scan shows a visible discontinuity of the esophagogastric wall (arrow). (D) CT-scan shows a mediastinal air cavity after esophagectomy (arrow). CT, computed tomography.

However, endoscopy has proven to be an accurate method to diagnose anastomotic leakage after esophagectomy (29). Thereby, an international survey showed that routinely performed endoscopy postoperatively is used by several surgeons (30). A study comparing endoscopy with CT in identifying anastomotic leakage after esophagectomy showed a more accurate identification of anastomotic leak than CT (31). Besides identification of the presence and location of leaks an endoscopy also provides more precise information on the condition of the gastric conduit. However, it provides no information about the mediastinal involvement, for which a CT scan is recommended. In our institute we first perform a CT scan to detect a possible anastomotic leakage. If inconclusive or if further treatment is warranted, we will proceed to perform an endoscopy. This can facilitate an immediate treatment of anastomotic leakage, for example by placement of an endoscopic endoluminal vacuum therapy, a nasogastric tube through the defect, or placement of an esophageal stent.

Conclusions

Esophagectomy with *en-bloc* lymphadenectomy after neoadjuvant chemo(radio)therapy is the standard of care for resectable locally advanced esophageal cancer. Postoperative complications may have a significant impact on the duration of hospital stay and quality of life. Intensive monitoring of the patient as part of a standardized ERAS program can help in early detection of complications, such as anastomotic leakage. In addition, an aggressive approach should be applied to both diagnose and treat anastomotic leakage. This may reduce failure to rescue rates and improve postoperative outcomes. However, an international guideline on the diagnostic and therapeutic management of anastomotic leakage is warranted.

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Footnote

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