Chyle Leakage after Esophageal Cancer Surgery

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Surgeons recommend dissecting lymph nodes in the thorax, abdomen, and neck during surgery for esophageal cancer because of the possibility of metastasis to the lymph nodes in those areas through the lymphatic plexus of the esophageal submucosal layer. Extensive lymph node dissection is essential for accurate staging and is thought to improve survival. However, it can result in several complications, including chyle leakage, which refers to continuous lymphatic fluid leakage and can occur in the thorax, abdomen, and neck. Malnutrition, fluid imbalance, and immune compromise may result from chyle leakage, which can be potentially life-threatening if it persists. Therefore, various treatment methods, including conservative treatment, pharmacological treatment such as octreotide infusion, and interventions such as thoracic duct embolization and surgical thoracic duct ligation, have been applied. In this article, the risk factors, diagnosis, and treatment methods of chyle leakage after esophagectomy are reviewed.

Keywords: Chyle leakage, Esophageal neoplasms, Esophagectomy, Chylothorax, Chyloperitoneum

Introduction

Esophageal surgery is an invasive procedure used to treat esophageal cancer. This procedure involves esophagectomy; extensive lymph node dissection at the thorax, abdomen, and neck; and reconstruction of the gastrointestinal tract. The morbidity rate after esophagectomy has been reported to be 50% based on a large-scale database [1,2]. Chyle leakage is a relatively rare complication, but it can be potentially life-threatening. If left untreated, it may result in hyponatremia, hypoproteinemia, edema, and malnutrition with decreased immune function, which may contribute to sepsis and increased mortality [3]. Therefore, the immediate diagnosis and treatment of chyle leakage after esophagectomy are very important. In this article, we review the diagnosis, risk factors, and treatment of chyle leakage after esophagectomy.

Anatomy of the thoracic duct

The thoracic duct is the primary structure that returns chyle from both sides of the body below the diaphragm to the venous circulation. It is approximately 36–45 cm long and 2–3 mm wide. It originates from the cisterna chyli in the abdomen, which is formed by the confluence of the 2 lumbar lymphatic trunks and the intestinal trunk. It enters the chest through the aortic hiatus between the azygos vein and the aorta in the right chest, crosses to the left chest at the level of the fifth thoracic vertebra, and enters the left jugulo-subclavian venous junction (Fig. 1). The lymphatic flow of the abdomen, left side of the face, hemithorax, and upper extremity runs into the left jugulo-subclavian venous junction, whereas that from the right side of the face, hemithorax, and upper extremity runs into the right jugulo-subclavian venous junction. The thoracic duct route is estimated to be typical in 40%–60% of all cases, while the other 40%–60% of patients have anatomic variations of the thoracic duct [4] (Fig. 2A). In addition, there are so many anatomical variations at the thoracic duct course and around the bilateral subclavian vein (Fig. 2B, C) that injury and subsequent leakage of unrecognized thoracic duct tributaries during transthoracic esophagectomy may put the patient at an increased risk of postoperative chyle leakage [5]. This is one reason why surgeons sometimes damage the thoracic duct during surgery despite vigilance. The thoracic duct has numerous valves that maintain the uni-
directional flow of chyle, and normal respiration helps pump the chyle toward the venous circulation. Similar to the medium or large-sized vessels, the thoracic duct has a smooth, contractile muscle layer.

**Physiology of chyle**

Approximately 2.4 L of chyle is transported through the lymphatic system every day. The primary role of the thoracic duct is to carry 60%–70% of ingested fat at a concentration of 0.4–6 g/dL from the intestine to the circulatory system [6]. Chyle is composed of lymphatic fluid and chylomicrons from the gastrointestinal system. Its lymphatic fluid contains protein, white blood cells, electrolytes, fat-soluble vitamins, trace elements, and glucose absorbed from the interstitial fluid to be returned to the systemic circulation [7]. Lymph is the other main constituent of chyle and is made up of immunoglobulins, enzymes, digestive products, and 400–6,800 white blood cells/mL, the majority of which are lymphocytes. Chylomicrons consist
of esterified monoglycerides and fatty acids combined with cholesterol and proteins. These are formed from the breakdown products of long-chain fatty acids by bile salts and absorbed into the lymphatic system through special lymphatic vessels in the villous region of the intestines, known as lacteals. Conversely, the smaller short- and medium-chain fatty acids are more water-soluble and are absorbed via the intestinal mucosa directly into the hepatic portal vein, bypassing the lymphatic system. To prevent retrograde flow, chyle is propagated within the thoracic duct primarily by the muscular action of breathing and further facilitated by the duct’s smooth muscles and internal valves. Factors that modulate chyle flow include diet, intestinal function, physical activity, respiration rate, and changes in the intra-abdominal and intra-thoracic pressure [8].

**Diagnosis of chyle leakage**

In patients experiencing chyle leakage, the fluid that is drained from the chest tube or Hemovac is often milky in appearance. The drain fluid color and characteristics are unique, but the diagnosis must be made based on laboratory findings and not by visual inspection. Another cause of milky-appearing drainage is pseudochyle, also known as cholesterol and chyliform effusions, which are cholesterol- and triglyceride-rich fluids associated with chronic inflammatory disorders [9,10]. Pseudochyle is clinically defined as the combination of a milky pleural effusion, a pleural cholesterol level greater than 200 mg/dL, a pleural triglyceride level typically below 110 mg/dL, a pleural cholesterol/triglyceride ratio of greater than 1, and often the presence of cholesterol crystals on microscopy [9,11,12]. The following diagnostic criteria must be met for chyle leakage to be diagnosed: triglycerides >110 mg/dL, cholesterol <200 mg/dL, and presence of chylomicrons. However, the above criteria may not be met when the patient is fasting, and the drainage color can be serous with a normal level of triglycerides. If the drainage volume from the chest tube or other tubes is large and does not diminish over time, chyle should be suspected first after esophagectomy, and an accurate diagnosis should be made after the initiation of oral intake.

**Chylothorax**

Chylothorax is a relatively uncommon, but well-known complication after esophagectomy. Despite improvements in operative strategies for esophageal cancer, the incidence of chylothorax is approximately 1.1%–21% in patients who undergo esophagectomy [13,14]. Chylothorax occurred in 7 (1.3%) of 536 patients who underwent esophagectomy for esophageal cancer between July 2006 and June 2019 at Severance Hospital. Of the patients with chylothorax, 3 were treated with surgical thoracic duct ligation, 2 with embolization, and 2 with conservative treatment.

**Risk factors for chylothorax**

The risk factors for chylothorax have been reported in many studies. Usually, extensive lymph node dissection and sometimes en bloc resection of the thoracic ducts are recommended in esophageal cancer surgery for oncologic reasons. With the increase of surgical extent, the risk of injuries in the main thoracic duct or thoracic tributaries is increased. Usually, the thoracic duct is more prone to damage if a patient has a higher clinical TNM (tumor-node-metastasis) stage because the tumor borders the thoracic duct more closely at a higher clinical stage [15]. The impact of neoadjuvant therapy for the treatment of esophageal cancer on postoperative chylothorax incidence is unknown and controversial. Gupta et al. [16] evaluated 45 patients with esophageal cancer who underwent esophagectomy after neoadjuvant chemoradiotherapy and reported that difficult mediastinal dissection during esophagectomy in middle esophageal cancer may result in thoracic duct injuries, and a complete response to neoadjuvant chemoradiation may reduce the risk of chylothorax. Gronnier et al. [17] outlined the results from a European multicenter study and suggested that neoadjuvant chemoradiotherapy increased chylothorax rates, with a trend toward more cardiovascular and thromboembolic events. Preoperative radiation to the mediastinum may damage the local lymphatic system and consequently delay the healing of small lymphatic vessel stumps caused by lymphadenectomy in the affected region, thereby causing chylothorax. In some cases, the primary tumor and a tumor embolus directly invade and erode the thoracic duct, and when the pressure of the tumor distends the thoracic duct tributaries, the weak spots can rupture [18]. It may be argued that chemoradiotherapy increases the incidence of postoperative chylothorax.

Other risk factors may cause chylothorax. Miao et al. [19] found that the incidence of chylothorax was 2.6% in 1,290 patients who underwent esophagectomy, and those with a body mass index (BMI) <25 kg/m² were more likely to develop chylothorax. Weijs et al. [14] reported that the independent risk factors for chylothorax after esophagectomy...
were the transthoracic approach, neoadjuvant chemoradiotherapy, and preoperative BMI. Ohkura et al. [20] found that balanced or negative intraoperative fluid balance reduced the incidence of postoperative chylothorax. They reduced the intraoperative fluid balance to meet the target value, which was less than 6.55 mL/kg/hr, and found that fluid management at a lower rate may be beneficial in preventing chylothorax. Moreover, they explained that excess perioperative fluid accumulation resulted in elevated interstitial fluid volume, and the consequent increase in the pressure inside the lymphatic vessels and thoracic duct made them leak-prone.

Some authors advocate routine intraoperative thoracic duct ligation to prevent chylothorax. Lin et al. [21] analyzed 296 patients who underwent esophagectomy, and the patients who underwent thoracic duct ligation showed lower chylothorax incidence (9.1% versus 0%, p<0.01). However, Lei et al. [22] disclosed the results of a meta-analysis on the effect of prophylactic thoracic duct ligation. In their report, no significant difference was found in postoperative chylothorax incidence between the patients who did and did not undergo prophylactic duct ligation [22]. Occasionally, irrespective of whether the thoracic duct is preserved or resected in esophagectomy, chylothorax still occurs even when the thoracic duct is ligated or clipped. One reason for this is the looseness of the ligation or slippage of the clips, and other reasons include anatomical variations and unidentified abdominal or thoracic tributaries of the thoracic duct that are injured during the operation.

## Conservative treatment

There is no standard therapeutic strategy for chylothorax because of the lack of prospective randomized trials evaluating the available treatment options, which mainly depend on physicians’ and surgeons’ experience [15]. The proposed treatment methods for chyle leakage are summarized in Table 1. Initial chylothorax treatment is usually conservative. The cornerstone of treatment is adequate fluid and electrolyte replacement, along with appropriate nutrition (with total parenteral nutrition [TPN] or medium-chain triglyceride [MCT] diet), drainage of the effusion, and prophylactic antibiotics. Due to the potential of high-volume fluid shift with protein and electrolyte loss caused by chyle leakage, patients with chylothorax need to be monitored for dehydration and malnutrition. Nutritional status, fluid, and electrolyte balance should be checked to avoid nutritional deficiency or further complications. Intravenous fluids including TPN should be administered to achieve eu- volemia and electrolytes should be replenished as needed. Dietary management plays a crucial role in conservative chylothorax treatment. During the period of chyle leakage, the authors usually use the MCT diet at first, followed by TPN if the drainage does not decrease [23]. Nevertheless, others recommend using TPN initially. Benedix et al. [24] reported that triglyceride and chylomicron levels in drainage fluid can rise on an MCT diet and water-only diet and increase output drainage by 20% in some patients. Even with an MCT diet, if a patient shows high chyle output, strict fasting with TPN that completely bypasses the lymphatic system is usually recommended. The use of TPN must be carefully weighed against its need for central venous access, the potential complications of infection and venous thrombosis, metabolic disturbances, and its high cost [25]. Patients are generally advised to consume a low-fat and MCT diet [26]. In general, an MCT diet with pro-

### Table 1. Treatments for chyle leakage after esophagectomy

<table>
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<td>Fluid replacement; IV nutrition; diet (MCT diet or NPO); clamping the drainage tube at the abdomen or neck if the patient finds it tolerable</td>
<td>Octreotide/ Sandostatin; Etilerine; Orlistat</td>
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IV, intravenous; MCT, medium-chain triglycerides; NPO, nil per os; OK-432, Picibanil.
tein, metabolic mineral mixture, and multivitamin supplementa-
tion is preferable to a nonfat diet. Because the MCT diet is largely water-soluble and absorbed via the portal ve-
nous circulation rather than the gastrointestinal lymphat-
ics, this special diet bypasses the gastrointestinal lymphatic
system, reducing chyle leakage and allowing the thoracic
duct injury to heal faster [27]. If the MCT diet cannot be
 taken orally, MCT powder can be administered through
jejunostomy or Levin tubes.

Pharmacologic treatment

In addition to conservative treatment, several pharma-
ologic agents can be considered simultaneously. Somatosta-
tin is a neuroendocrine hormone discovered in 1973, with
numerous effects on the digestive and lymphatic systems
[28]. Two possible mechanisms through which somatosta-
tin ameliorates chyle leakage have been suggested. Soma-
tostatin decreases chyle production via the reduction of
gastric, pancreatic, and intestinal secretions [29]. It also
constricts smooth muscles in the splanchnic and lymphatic
vessels to decrease lymph production [23] and lymph flow
[30], respectively. A major drawback of somatostatin is its
short half-life, which requires continuous intravenous in-
fusion. This problem was solved with the development of
octreotide, a long-acting analog of somatostatin, which can
be administered through long-lasting subcutaneous injec-
tions [31]. To date, there are no consensus guidelines on
the optimal octreotide treatment dose and duration in chy-
lothorax management. In previous papers, octreotide dos-
age ranged from 100 μg (subcutaneous) every 8 to 12 hours
to 200 μg (subcutaneous) every 8 hours [32]. Furthermore,
some clinicians have infused octreotide continuously. The
time from octreotide therapy initiation to chyle leakage
cessation varied from 1–15 days, and the total octreotide
treatment duration varied widely from 3–24 days. In gen-
eral, octreotide is administered for an additional 1–2 days
after chyle leakage cessation to ensure complete resolution.
The most common side effects of octreotide are nausea,
abdominal discomfort, and diarrhea. Rare but serious
complications include hypoglycemia and cholecystitis sec-
ondary to cholestasis. In fewer than 1% of patients, an-
aphylactic shock, gastrointestinal bleeding, and pulmonary
embolism have been described. Octreotide should be pre-
scribed with caution in patients with preexisting cardio-
vascular and hepatic diseases [31]. Most adverse effects are
do-se- and duration-dependent.

Etilerine is a sympathomimetic drug used in postural
hypotension [33]. It causes smooth muscle fiber contrac-
tion in the thoracic duct, similar to somatostatin [34], re-
sulting in the reduction of the amount of chyle and repair
of the injury sites. Etilerine has a few side effects including
headache, tachycardia, anxiety, and flushes [35]. Unfortu-
nately, etilefrine is not currently available in South Korea.
Orlistat, a pancreatic lipase inhibitor, interferes with lipid
metabolism in the duodenum and prevents lipid absorp-
tion and may be given as an adjunct to decrease chyle pro-
duction [36], but it is not available in South Korea. Pleu-
rodesis with chemical agents such as talc can be performed
in addition to conservative and pharmacologic treatments.

Interventions: thoracic duct ligation and
embolization

Most patients with chyle leakage recover after conserva-
tive treatment. However, the authors consider invasive
treatments if chylothorax persists. The timing of invasive
procedures is controversial. Usually, the amount of drain-
age, duration, and the patient’s condition must be taken
into account. Selle et al. [37] recommended an operation to
ligate the thoracic duct when chyle leakage persists for at
least 5 days at the rate of 1,500 mL/day or more in adults
and when the drainage of chyle does not decrease within
2 weeks or the patient’s nutritional or metabolic status be-
comes measurably more impaired during the same period.
The authors also have experienced secondary infections in
patients with chylothorax related to immune compromise,
which can be an important criterion for deciding upon an
invasive procedure [38].

Surgical ligation of the thoracic duct is a classical meth-
од to treat chylothorax. The thoracic duct is found between
the descending thoracic aorta and azygos vein. Fatty fluid
infusion via a Levin tube, before or during the operation,
aids in finding the leakage point. If the leakage point is
noted, the proximal area of the thoracic duct can be ligated
with a suture or clip. Ligation at the diaphragm level is
generally recommended. This procedure usually can be
done through a right-side approach. Because most previous
reports on surgical ligation of the thoracic duct were case
series, the exact success rate is difficult to quantify, but
chylothorax can usually be treated if ligation is properly
executed [39].

Recently, thoracic duct embolization has replaced surgi-
cal thoracic duct ligation for the treatment of chylothorax.
Thoracic duct lymphangiography can be done by inguinal
lymphangiography. Under direct ultrasound guidance,
physicians identify and assess superficial inguinal lymph
nodes. Consecutive fluoroscopic spot images are obtained
until contrast is seen coursing cranially and opacifying the cisterna chyli or the thoracic duct. If extravasation of contrast material is identified, embolization of the thoracic duct with a liquid embolic agent (Lipiodol) and/or coils is performed across or proximal to the leak point [40]. The success rate of thoracic duct embolization depends on the institutional experience and has been reported to be 45%–78% [41]. Lower extremity edema and chronic diarrhea are the most frequent significant complications that arise from thoracic duct embolization [42]. Because thoracic duct embolization does not require general anesthesia, it can be performed more easily than surgical thoracic duct ligation. After introducing thoracic duct embolization at our institution, we make quick decisions to perform embolization without long periods of observation.

Chyloperitoneum

Chyloperitoneum is defined as a milky-appearing, triglyceride-rich peritoneal fluid characterized by the presence of thoracic or intestinal lymph in the abdominal cavity [43]. Studies have determined various etiologies of chyloperitoneum, such as abdominal malignancy; liver cirrhosis, infection, or inflammation; or trauma, including abdominal lymph node dissection. In cases of esophagectomy, abdominal lymph node dissection might be related to chyloperitoneum. Of particular note, the celiac axis and common hepatic lymph node dissection during esophagectomy is related to chyloperitoneum. The authors always check the dissected area of the celiac axis and common hepatic lymph nodes at the end of the operation, and if the leakage is suspected, these areas are sealed and closed with non-absorbable sutures. The exact incidence of chyloperitoneum have not been reported due to its rarity. At Severance Hospital, its incidence is only 0.56% (4 cases) from July 2006 to June 2019. Three of these cases were treated with conservative treatment, and an OK-432 injection was administered in 1 case.

Treatment of chyloperitoneum

The treatment of chyloperitoneum is similar to that of chylothorax, especially regarding conservative and pharmacologic treatments. The abdominal cavity pressure is always positive, whereas the intrathoracic pressure is always negative. Clamping of the drainage tube could be effective, unless the patient shows abdominal discomfort, dyspnea, or secondary pleural effusion. Sometimes, the increased abdominal pressure might obliterate the chyle leakage in the abdomen. Patients with clinical symptoms due to chyloperitoneum require repeated paracentesis or drainage to decrease the discomfort related to the increased intra-abdominal pressure and the concomitant respiratory insufficiency caused by the large abdominal fluid collection, the impaired venous return, and the displaced diaphragm. Additional treatment options could be applied. A sclerosing agent can be injected into the suspicious leakage point. Inaba et al. [44] reported the local intraperitoneal administration of OK-432 (Picibanil) using a unified computed tomography and fluoroscopy system for the treatment of chyloperitoneum after gastrectomy, and this technique can be applied after esophagectomy. The authors also applied this procedure successfully in the case of chyloperitoneum after esophagectomy and abdominal lymph node dissection. Some previous case reports have stated that low-dose radiation therapy at the cisterna chyli can relieve chyloperitoneum [45]. Brown et al. [45] reported a patient who was treated with a dose of 10 Gy in daily 1-Gy fractions to the para-aortic region, including the cisterna chyli and thoracic duct from T12 to L2. Low-dose ionizing radiation exhibits anti-inflammatory and apoptotic effects that cause fibrosis or scarring of tissue after trauma, and low-dose radiation can therefore obliterate the chyle leakage point. A peritoneo-jugular shunt (Denver or LeVeen shunt) can also be a good treatment option for chyloperitoneum. Chyle is aseptic in nature and can be drained into the systemic venous circulation by the peritoneo-jugular shunt. However, these shunts are not commercially available in South Korea [46]. A transjugular intrahepatic portosystemic stent shunt creates a communication between the portal and systemic circulation within the liver. By reducing portal pressure, it can relieve lymphatic hypertension [47]. Surgical ligation of the leakage point in cases of chyloperitoneum is technically challenging. It must be considered the last treatment modality because of its high probability of failure. Preoperative lymphangiography or lymphoscintigraphy is helpful in identifying the anatomical location of the leakage or the presence of a fistula. Matsutani et al. [48] reported a case in which the transabdominal approach was successfully used for chyloperitoneum after esophagectomy by using fluorescence navigation with indocyanine green. They injected indocyanine green in the inguinal lymph nodes, as in thoracic duct lymphangiography, and they documented the chyle leakage points under a fluoroscopic camera. Even though these novel techniques can be helpful, an exploratory laparotomy should be performed as a last resort. In addition, cisternal chyli embolization for
chyloperitoneum is not usually performed [41].

Chyle leakage at the neck

Because the exact incidence of chyle leakage after esophagectomy has not been reported, we can infer its incidence from the results of head and neck surgery as 0.5%–1.4% of thyroidectomies [49,50] and 2%–8% of neck dissections [51,52]. If the surgeons perform 3-field lymph node dissection, chyle leakage at the neck theoretically occurs in 2%–8% of cases, but the real chyle leakage incidence after esophagectomy might be lower than that assumption. If the amount of neck drainage increases, especially after enteral feeding, and if erythema, lymphedema, or palpable fluid collection is observed in the supraclavicular area, chyle leakage can be strongly suspected [27]. Usually, the drainage color is creamy or milky; however, the drainage can be serous if the thoracic duct is ligated. In addition, chyle leakage of the right side of the neck can be serous even if the patient consumes a normal meal.

Treatment of chyle leakage at the neck

Conservative treatment is similar to the chylothorax and chyloperitoneum. Especially in the neck, clamping of the drainage tube can be effective, but lymphocele can form at the leakage point. In addition to conservative treatment, sclerosing agents such as OK-432 or tetracycline administered at the time of surgery or postoperatively through a drainage tube or percutaneous injection can generate fibrosis to seal chyle leakage at the neck [53]. Sclerotherapy should be used with care, as it can potentially injure the surrounding structures in the wound bed. Phrenic nerve paralysis after doxycycline sclerotherapy for chyle leakage has been reported [54]. Furthermore, the authors have experienced Horner syndrome after OK-432 injection into the neck. Transcervical lymphangiography also can be done either by a direct approach to the lymphocele or a retrograde approach from the cephalic vein [41]. Additionally, Kadota et al. [55] described the successful use of negative pressure wound therapy (NPWT) for postoperative chyle leakage after neck dissection. NPWT is thought to facilitate fluid extraction from the wound bed and surrounding interstitial space, thereby hastening granulation tissue formation and minimizing dead space [56]. They used a relatively a low pressure (50 mm Hg) to avoid an unwanted increase in drainage because of the negative pressure, and the leakage resolved within 6 days. Notably, massive bleeding occurred when NPWT had been applied around major vessels [57]. Kadota et al. [55] avoided this complication by using gauze to cover the tip of the tube connected to the NPWT device and the soft tissues encompassing the major vessels and microsurgical anastomoses. NPWT is another treatment option for chyle leakage after neck dissection. It is minimally invasive, is less burdensome to patients, and can be applied in intractable cases when other conservative treatments fail [23].

Surgical re-exploration should be considered only after conservative treatment has either been exhausted or deemed ineffective. Although the recommended criteria for re-exploration vary considerably, the general consensus is that surgical re-exploration should take place when chyle leakage does not respond appropriately to conservative management. At the time of re-exploration, local inflammation from extravasated chyle can make thoracic duct identification difficult. Trendelenburg positioning and the Valsalva maneuver, which raise the intra-thoracic and intra-abdominal pressure, can facilitate the identification of the site of chyle leakage. Furthermore, providing the patient with a fatty diet before surgery can stimulate chyle production and aid in the localization of the leakage point. As described above, when identified, the leaking point can be ligated, covered with a muscle flap, or treated with any number of sclerosing agents, adhesive agents, or mesh.

Conclusion

Chyle leakage is uncommon, but it can be a serious complication of esophageal cancer surgery. Chyle leakage can result in dehydration, malnutrition, electrolyte disturbances, and immunosuppression. For the diagnosis, the characteristics and laboratory findings of the fluid are essential. Furthermore, it is important to consider the possibility of chyle leakage if the amount of drainage is high, even if the drainage is serous. Conservative treatments with pharmacologic agents are essential. The development of thoracic duct embolization has enabled surgeons to decide whether to perform an invasive procedure more affirmatively and actively, minimizing the potential surgical risk.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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