



## Risk factors of chylothorax after esophagectomy

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Chylothorax is a relatively uncommon but well-known complication after esophagectomy. Despite improvements in operative strategies for esophageal cancer, the incidence of chylothorax is about 1.1% to 21% in patients who receive esophagectomy (1,2). Though this condition is not rare, it is also dire and may lead to the inhibition of lung function, malnutrition, and immunologic compromise. It is, therefore, a potentially dangerous complication. Many studies aiming at therapeutic strategies of postoperative chylothorax have been introduced, but few studies have investigated the risk factors of this condition.

In the issue of *Annals of Oncology*, Ohkura and his colleagues (3) conducted a retrospective study, of which 93 patients underwent esophagectomy with thoracic duct (TD) preservation and 201 patients underwent esophagectomy with TD resection. Twenty-four patients suffered from chylothorax after esophagectomy. Among them, 3 had TD preservation, and the remaining 21 underwent TD resection. They found a significant difference in three factors between the chylothorax patients and the non-chylothorax patients. The study indicated that resection of the TD, post chemoradiotherapy, and high intraoperative fluid balance would affect the incidence of postoperative chylothorax after esophagectomy. In the meantime, post chemoradiotherapy and high intraoperative fluid balance are predictors of chylothorax after esophagectomy.

In this study, unlike routine prophylactic ligation of the TD at the time of esophagectomy, they combined TD

resection with TD ligation rather than prophylactic TD ligation without TD resection. They did not ligate TD for those patients receiving TD preservation. In their paper, they concluded that the rates of chylothorax were higher in the TD resection group compared with the TD preservation group ( $P=0.035$ ). In contrast, Matsuda *et al.* (4) compared the number of dissected lymph nodes, surgical outcomes, and postoperative recurrence-free survival between TD resection and TD preservation groups in patients with esophageal squamous cell carcinoma who underwent transthoracic esophagectomy. They found that there was no significant difference in the incidence of postoperative complications, including pneumonia, anastomotic leakage, and chylothorax. Other studies reached no consensus on this issue.

As we know, the TD is the main conduit of the lymphatic system, and it originates from the cisterna chyli in the abdomen that is formed by the confluence of the two lumbar lymphatic trunks and the intestinal trunk. It enters the chest through the aortic hiatus between the azygous vein and the aorta in the right chest, crosses to the left chest at the level of the fifth thoracic vertebrae, and enters the left jugulo-subclavian venous junction. This typical route of the TD is estimated to be found in 40–60% of all cases. At the same time, anatomic variations of the TD also account for 40% to 60% of patients (5). Defize *et al.* (6) dissected the TD and its tributaries in embalmed human cadavers and found that the TD was formed in the thoracic cavity in conjunction with multiple abdominal tributaries. It does not pass the

diaphragm as a single TD. Moreover, there are some anatomic lymphaticovenous shunts in the TD tributaries in some patients. There are so many variations in TD anatomy that injury and subsequent leakage of unrecognized TD tributaries during transthoracic esophagectomy may put the patient at increased risk of postoperative chylothorax.

Like Ohkura and his colleagues, many esophageal surgeons, especially oncologic surgeons recommend the extension of dissection including the TD in esophagectomy for oncological reasons. With the extension of surgical scope, the risk of injuries in the main TD or thoracic tributaries is increased, which raises the incidence of chylothorax related to esophagectomy. Some authors advocate routine ligation of the TD to prevent chyle leakage (7). Occasionally, whether the TD is preserved or resected in esophagectomy, thoracic chyle leakage still occurs even when the TD is ligated or clipped. One reason is looseness of the ligation or slippage of the clips, and another reason is that unidentified abdominal or thoracic tributaries of the TD are injured during the operation.

Most of the time, the TD is more prone to damage if a patient has a higher clinical TNM stage, because of the tumor outskirts the TD more closely at a higher clinical stage. In Table 1 (3), as far as cStage is concerned, there was no significant difference between every stage, but with the development of the disease, we would see an incremental trend toward incidence of postoperative chylothorax. According to the data available from the table, the incidence of chylothorax in stage I, II, III and IV was 6.4%, 4.8%, 11.1%, and 18.8%, respectively. Sometimes, any damage which occurs in the main TD may be more easily recognized and ligated at the time of the original operation, because lymphatic fluid would flow from the injury site and be easily identified.

Since the introduction of neoadjuvant therapy in the treatment strategies of esophageal cancer, its impact on the incidence of postoperative chylothorax is unknown, especially for the irradiation injury to the TD. Gupta *et al.* (8) evaluated the data of 45 patients of esophageal carcinoma who underwent esophagectomy after neoadjuvant chemoradiotherapy. They found that difficult mediastinal dissection during esophagectomy in middle esophageal cancer may lead to TD injury, and complete response to neoadjuvant chemoradiation may reduce the risk of chylothorax. In Ohkura's article, one-third of chylothorax patients received neoadjuvant chemoradiation or definitive chemoradiotherapy. However, how many patients acquired a complete response? Moreover, was the result consistent

with Gupta's findings?

The lymphatic system damage after chemoradiotherapy is the primary consideration for postoperative chylothorax. Thomson *et al.* (9) described that radiotherapy could cause narrowing of lymph vessels and consequent impaired lymph flow. Gronnier *et al.* (10) got results from a European multicenter study and suggested that neoadjuvant chemoradiotherapy increased chylothorax rates with a trend toward more cardiovascular and thromboembolic events. As pointed out by the authors, preoperative radiation to the mediastinum may damage the local lymphatic system and consequently delay the healing of stumps of small lymphatic vessels caused by lymphadenectomy in the affected region, thereby causing chylothorax. Moreover, it is difficult to separate esophagus from the surrounding mediastinal structures because the esophagus lies in the radiation range and will always receive some radiation. Sometimes, the primary tumor and a tumor embolus would directly invade and erode the TD, and when the pressure of the tumor distend the TD tributaries, the weak spots can rupture. Therefore, chylothorax occurs. Reasons listed above will increase the risk of intraoperative injury of the TD and lead to postoperative chylothorax.

However, some studies manifested that there was no increase for patients receiving neoadjuvant chemoradiotherapy in terms of postoperative chylothorax (11,12). Furthermore, Yang *et al.* (13) compared the survival and safety of neoadjuvant chemoradiotherapy plus surgery with surgery alone in patients with locally advanced esophageal squamous cell carcinoma. They did not find any differences in postoperative chylothorax in two groups. It may be argued that chemoradiotherapy increases the incidence rate of postoperative chylothorax.

In this study, Ohkura and his colleagues described an exciting phenomenon that Intraoperative fluid balance would reduce the incidence of postoperative chylothorax. With the assistance of anesthesiologists, they reduced the intraoperative fluid balance to meet the target value which was less than 6.55 mL/kg/h and found that fluid management at a lower rate may be beneficial in preventing chylothorax. They made a further explanation that excess perioperative fluid accumulation resulted in elevated interstitial fluid volume. A consequent increase in pressure inside the lymphatic vessels and TD will make them leak-prone, and the slight damage during esophagectomy may result in chylothorax. In another study, Imamura *et al.* (14) described that resection of the TD does not seem to influence the hemodynamics or the lymphatic dynamics in

the late postoperative days, but they found resection of the TD did affect postoperative hemodynamics during surgery and within 48 h after surgery. The patient who underwent an *en bloc* resection of esophageal cancer including the TD needs a significantly larger amount of plasma or electrolyte solutions than those patients whose TD are not resected. It is a pity that they did not mention the incidence of chylothorax in these esophageal cancer patients. In a similar study, Anand and his colleagues (15) conducted a study to assess the hemodynamic changes following TD resection in esophageal cancer patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy. Patients were divided into TD-resection and TD-preservation groups, and they reported that one patient in the TD-resection group had chylothorax due to slippage of clips that was managed successfully by thoroscopic re-exploration and ligation. According to this study, minimally invasive esophagectomy with TD resection resulted in transient hemodynamic disturbances in the immediate postoperative period, and there was no difference in chyle leak between two groups, the P value was 0.292. Just like the authors said, the small sample size is the major limitation of the study, only 22 patients are enrolled in this study.

Although fluid management at a lower rate (less than 6.55 mL/kg/h) may be beneficial in preventing chylothorax, the infusion volume described by Ohkura and his colleagues appeared too small. As Imamura *et al.* (14) described in their study, severe shock took place immediately after *en bloc* resection of the esophagus when the standard rate (8 mL/kg/h) of infusion of electrolyte solution or plasma was used during surgery in two patients. Massive infusions of plasma and electrolyte solution counteracted shock in these patients. It is obviously that Ohkura and his colleagues used less infusion volume than what Imamura *et al.* did. Did hemodynamic parameters fluctuate violently in TD-resection patients with fluid management at a lower rate in this study? Does the intraoperative fluid balance have an influence on the incidence of postoperative chylothorax after esophagectomy? There is still room to talk about the particular issue.

Apart from the three factors that the authors have listed, some other risk factors may cause chylothorax. In our large-cohort study, we found that the incidence of chylothorax was 2.6% and patients with a body mass index (BMI) <25 were more likely to develop chylothorax after esophagectomy (16). Weijs *et al.* (2) thought that independent risk factors of chylothorax

after esophagectomy were a transthoracic approach, neoadjuvant chemoradiotherapy, and preoperative BMI.

Taken together, chylothorax is a dire and concerning situation for patients after esophagectomy. It would be devastating if not addressed promptly. Chylothorax should be suspected when there is an unexplained high-volume chest tube output. Once the diagnosis is confirmed early medical intervention is critical. There is no standard therapeutic strategy for chylothorax because of lacking prospective randomized trials which evaluate the available treatment options. Most patients with chyle leakages can recover after conservative treatments. However, surgery remains necessary for a minority of patients with chyle leaks. Conservative treatments include a low-fat diet, total parenteral nutrition, and octreotide. Pleurodesis, lymphangiography followed by coiling and embolization, even radiotherapy represent acceptable alternatives (17). Surgical intervention is indicated if initial conservative treatment failed, and thoracotomy or thoracoscopy ligation of the duct should be considered.

Identifying the risk factors of chylothorax is still a controversial topic and not clearly understood. We may not foist responsibility for chylothorax onto chemoradiation, resection of TD or anything else. Chyle leak may occur from aberrant sites, and the injuries of the main TD or its tributaries may play a key role in postoperative chylothorax. We look forward to prospective randomized controlled trials to clarify the issue.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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