Ann Surg Oncol (2018) 25:2739–2746
https://doi.org/10.1245/s10434-018-6640-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Risk Factors for Postoperative Chylothorax After Radical Subtotal Esophagectomy

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ABSTRACT

Background. Chylothorax is one of the complications of esophagectomy for esophageal cancer. The treatment of this condition has been well discussed, but the risk factors for postoperative chylothorax remain unclear.

Methods. A retrospective review of 294 patients who underwent esophagectomy for esophageal cancer was conducted. These were patients with squamous cell carcinoma or adenocarcinoma of the esophagus including Siewert type I tumor of the esophagogastric junction who underwent subtotal esophagectomy with two-field or three-field lymphadenectomy. Of these, 24 patients who were diagnosed with chylothorax as a postoperative complication were allocated to the chylothorax group and the other 270 patients were allocated to the nonchylothorax group.

Results. Univariate analysis showed a significant difference in three factors: resection of thoracic duct, post-chemoradiotherapy, and high intraoperative fluid balance. Multivariate analysis revealed that post-chemoradiotherapy [hazard ratio (HR) = 3.430; 95% confidence interval (CI) 1.364–8.625] and high intraoperative fluid balance (HR = 1.569; 95% CI 1.2.7–2.039) were independent factors predicting chylothorax. In addition, resection of the thoracic duct may be a predictor of chylothorax after esophagectomy (HR = 3.389; 95% CI 0.941–12.201, $p = 0.062$). Receiver operating characteristic curve analysis of intraoperative fluid revealed that the sensitivity was 62.5%, specificity was 74.1%, and the cutoff value was 6.55 mL/kg/h.

Conclusions. This study revealed that post-chemoradiotherapy and high intraoperative fluid balance are predictors of chylothorax after esophagectomy. The elucidation of clinicopathological factors that can predict the incidence of chylothorax will help to establish more effective perioperative management for esophageal cancer patients.

Esophagectomy for esophageal cancer is a highly invasive procedure associated with high incidence of complications and is one of several extremely delicate interventions in gastrointestinal surgery. Common complications include chylothorax, which occur in 2–12% of patients.[1–6] Several reports have described cases of postoperative chylothorax with emphasis on treatment.[1–6] However, few studies have investigated background considerations and risk factors, despite the potential benefit in identifying preventive interventions and measures. Thus, this study examined patients who had undergone radical subtotal esophagectomy for esophageal cancer to identify risk factors for postoperative chylothorax.

MATERIALS AND METHODS

Study Population

This single-center, retrospective study was conducted to evaluate the risk factors for postoperative chylothorax after esophagectomy. A total of 419 consecutive patients with esophageal cancer were identified from a database that was prospectively constructed between January 2011 and June 2017. Among these, 294 patients were selected according to the following inclusion criteria: histopathologically

First Received: 15 March 2018;
Published Online: 11 July 2018

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proven squamous cell carcinoma or adenocarcinoma; esophageal cancer from cervical esophagus to abdominal esophagus, including only Siewert type I tumor of the esophagogastric junction, who underwent subtotal esophagectomy with two-field or three-field lymphadenectomy; gastric tube or ileocolonic reconstructions; and curability A or B.[7] Of these 294 patients, 24 patients who were diagnosed with chylothorax as a postoperative complication were allocated to the chylothorax (C–), group and the remaining 270 patients were allocated to the nonchylothorax (N–) group. We investigated the risk factors for postoperative chylothorax after esophagectomy. From these results, we prospectively attempted to validation study of 52 patients who underwent esophagectomy at our hospital between July 2017 and February 2018, with the assistance of anesthesiologists. The intraoperative fluid balance was calculated using the following equation: (input–output balance during surgery)/(body weight)/(total anesthesia time) (mL/kg/h). Disease stage was classified according to the UICC TNM grading system, 7th edition.[8] We graded all postoperative complications based on the Clavien-Dindo classification, and grade ≥ 3 events were documented as complications.[9] This study (retrospective study and validation study) was conducted with approval from the Institutional Review Board of Toranomon Hospital (approval number 1657).

Preoperative Treatment

Of the patients, 128 had undergone neoadjuvant chemotherapy (NACT), 25 had undergone neoadjuvant chemoradiotherapy (NACRT), and 7 had undergone definitive chemoradiotherapy (DCRT). As shown in previous reports, DCRT was defined as chemotherapy combined with $\geq$ 50.4 Gy of radiation.[10,11] Chemotherapy regimens were FP (800 mg/m^2 of 5-fluorouracil (5FU) and 80 mg/m^2 of cisplatin), DCF (60 mg/m^2 of docetaxel, 50 mg/m^2 of cisplatin, and 500 mg/m^2 of 5FU), or SP (80–100 mg/day of tegafur/gimeracil/oteracil (S–1) and 60 mg/m^2 of cisplatin). Chemoradiotherapy regimens were FP or DCF.

Operative Procedure for Esophagectomy

We performed esophagectomy with two- or three-field lymph node dissection depending on the degree of progression and surgical risk involved.[7] The operative thoracic approach was by video-assisted thoracoscopic surgery (VATS) or thoracotomy, and the abdominal approach was hand-assisted laparoscopic surgery (HALS) or open laparotomy depending on individual cases. We generally preserved the thoracic duct (TD) in cases with clinical stage (cStage) I and performed its resection in cases with cStage $\geq$ II for the purpose of lymphadenectomy.[8] However, we resected TD when we suspected lymph node metastases, or we confirmed lymph node metastases to the bilateral recurrent nerve lymph nodes using intraoperative immediate pathological diagnosis, even if the case was cStage I. On the other hand, we tried to preserve TD in patients with high risk, particularly in hepatic or pulmonary function. A manually sutured esophagogastric or esophageal anastomosis in the neck was fashioned for all patients.[12–16]

Definition of Chylothorax

Chylothorax was suspected if there was excessive chest drain output (> 800 mL/day) and the color of chest drainage fluid turned milky white after tube feeding or oral ingestion. The pleural effusion was checked macroscopically to determine suspected chylothorax. We made a diagnosis of chylothorax according to the following criteria: pleural fluid triglycerides (TG) > 110 mg/dL, ratio of pleural fluid TG to serum TG > 1, and/or confirmation of chylomicrons in the pleural drainage when the value of pleural fluid TG 50-110 mg/dL.[17]

Management of Chylothorax

The protocol followed in our hospital involves application of a nutritional approach first, with patients receiving total parenteral nutrition. They are started on octreotide (300 µg/day) by continuous subcutaneous infusion and/or etilefrine (120 mg/day) by intravenous injection concurrently. If there is progressive resolution of the chylous pleural effusion with this treatment, and the effluent is approximately < 50–100 mL/day, we perform pleurodesis with OK-432. After that, the patient makes satisfactory progress and resumes oral food intake. If the effluent remains approximately less than 50–100 mL/day after oral food intake is started, the thoracotomy tube is removed. If conservative treatment fails (excessive chest drain output > 400–500 mL/day), we then consider more invasive treatment, such as lymphangiography, TD embolization, or TD ligation.

Statistics

Risk factors for postoperative complications following chylothorax were assessed by logistic regression analysis. Comparisons between groups were performed using the Mann–Whitney *U* test and Pearson's Chi squared test for statistical significance. Variables with significance of $p < 0.05$ in the simple Cox proportional hazards models were entered into multiple Cox proportional hazards models. In the multiple Cox proportional hazards models,

$p < 0.05$ was considered significant. All analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 19.0 J for Windows (SPSS Inc., Chicago, IL).

RESULT

Patients' Characteristics and Factors Predictive of Chylothorax in Univariate Analysis

Table 1 summarizes the patient characteristics of the two groups. Variables identified using simple Cox proportional hazards models were selected for potential association with chylothorax based on previous studies or our clinical experience. Univariate analysis between the N-group and the C-group showed a significant difference in three factors: resection of TD, post-chemoradiotherapy, and intraoperative fluid imbalance (toward excess). Mean length of postoperative hospital stay was significantly shorter in the N-group (23.8 days) than in the C-group (38.0 days; $p < 0.001$).

Postoperative Complications in Control Group

Postoperative CD grade ≥ 3 complications were observed in 61 of the 270 (22.6%) patients in the control group. There was no operative death in this study. Postoperative complications were cervical lymphorrhea ($n = 23$), anastomotic leakage ($n = 18$), bleeding ($n = 3$), and others ($n = 17$).

Treatment for Postoperative Chylothorax

Among 24 patients, 3 required surgical treatment, and the remaining 21 patients were cured with nonsurgical treatment. Of these, 5 patients had only the nutrition approach, 4 patients had only octreotide, 4 patients had octreotide and etilefrine, 8 patients underwent pleurodesis after treatment with octreotide and etilefrine, and 3 patients underwent surgical treatment after treatment with octreotide and etilefrine.

Factors Predictive of Chylothorax in Multivariate Analysis

Multivariate analysis using the results of univariate analysis (Table 2) was performed for the following selected variables: age, sex, resection of TD, post-chemoradiotherapy, and intraoperative fluid balance. Post-chemoradiotherapy [hazard ratio (HR) = 4.648; 95% confidence interval (CI) 1.690–12.779), and high intraoperative fluid balance (HR = 1.464; 95% CI 1.042–2.058) were all identified as independent factors predictive of chylothorax. Additionally, resection of TD may be a predictive factor of chylothorax (HR = 3.389; 95% CI 0.941–12.201; $p = 0.062$).

Receiver operating characteristic (ROC) curve analysis of intraoperative fluid balance revealed that the area under the curve (AUC) was 0.700 (95% CI 0.577–0.822; Fig. 1). For this ROC curve, sensitivity was 62.5%, specificity was 74.1%, and the cutoff value of intraoperative fluid balance was 6.55 mL/kg/h. Intraoperative fluid balance was < 6.55 mL/kg/h and $\geq$ 6.55 mL/kg/h in 209 and 85 patients, respectively. Of these 209 patients (< 6.55 mL/kg/h), only 9 (4.3%) were diagnosed with chylothorax, Conversely, of these 85 patients ($\geq$ 6.55 mL/kg/h), 15 patients (17.6%) were diagnosed with chylothorax.

Validation of the Intraoperative Fluid Balance Prospectively

From these results, we prospectively attempted to reduce intraoperative fluid balance to meet the target value (< 6.55 mL/kg/h) with the assistance of anesthesiologists for all patients who underwent esophagectomy. However, it is difficult to meet the target value for all patients. In fact, we calculated the intraoperative fluid balance after surgery. As a result, some patients did not meet the target value (< 6.55 mL/kg/h) unintentionally. We additionally report the results of a prospective study of 52 patients who underwent esophagectomy at our hospital between July 2017 and February 2018. Among these 52 patients, 5 patients developed postoperative chylothorax, and resection of TD was performed for all 5 of these patients. Two of these 5 patients underwent neoadjuvant chemoradiotherapy. Intraoperative fluid balance was < 6.55 mL/kg/h and $\geq$ 6.55 mL/kg/h in 34 and 18 patients, respectively. Of these 34 patients (< 6.55 mL/kg/h), only 1 (2.9%) was diagnosed with chylothorax. In contrast, of these 18 patients ($\geq$ 6.55 mL/kg/h), 4 patients (22.2%) were diagnosed with chylothorax ($p = 0.025$). ROC curve analysis of intraoperative fluid balance revealed that the AUC was 0.736 (95% CI 0.476–0.996) among these 52 patients.

DISCUSSION

In this study, we attempted to identify the factors predictive of postoperative chylothorax after esophagectomy. Multivariate analysis revealed that factors predictive of postoperative chylothorax were post-chemoradiotherapy and high intraoperative fluid balance. In addition, resection of TD may be a predictor of chylothorax after esophagectomy.

The incidence of chylothorax was significantly higher in patients who had undergone post-chemoradiotherapy but not in those who had undergone post-chemotherapy,

TABLE 1 Patient characteristics and univariate analysis of the 294 patients

	N group (n = 270)	C group (n = 24)	p value
(a)			
Age (year) median (range)	65.4 (29–84)	66.5 (43–77)	0.872
Sex			
Male	230	17	
Female	40	7	0.066
BMI	22.6 (15.2–41.9)	21.7 (16.8–29.2)	0.887
ASA			
1	50	5	
2	198	18	
3	20	1	0.835
Presence of dyslipidemia			
Yes	42	4	
No	228	20	0.886
cT factor			
T1a/1b	120	6	
T2	62	5	
T3	75	10	
T4a/4b	13	3	0.289
cN factor			
N0	138	10	
N1	85	9	
N2	47	5	0.794
cM factor			
M0	257	21	
M1	13	3	0.112
cStage (7th edition)			
I (IA, IB)	117	8	
II (IIA, IIB)	60	3	
III (AIII, IIB, IIIC)	80	10	
IV	13	3	0.226
Tumor localization			
Ce	4	1	
Ut	43	4	
Mt	131	15	
Lt	64	2	
Ae	8	1	
EGJ	20	1	0.472
Lymphadenectomy			
2-field	91	4	
3-field	179	20	0.087
Operative approach (thoracic)			
Open	35	6	
VATS	235	18	0.103
Operative approach (abdomen)			
Open	112	7	
HALS	158	17	0.239

TABLE 1 continued

	N group (n = 270)	C group (n = 24)	p value
Thoracic duct			
Preservation	90	3	
Resection	180	21	0.035
Reconstruction organ			
Gastric tube	162	16	
Ileocolon	108	8	0.522
Reconstructive route			
Retrosternal route	222	21	
Posterior mediastinal route	48	3	0.513
(b)			
Chemotherapy			
Yes	119	9	
No	151	15	0.534
Chemoradiotherapy			
Yes (NACRT/DCRT)	24 (19/5)	8 (6/2)	
No	246	16	0.002
Curability			
CurA	214	20	
CurB	56	4	0.635
pT factor			
T0	11	3	
T1a/1b	150	8	
T2	35	4	
T3	65	9	
T4a/4b	9	0	0.203
pN factor			
N0	142	11	
N1	74	7	
N2	54	6	0.238
Existence of mediastinal LN metastasis			
Yes	97	10	
No	173	14	0.575
Operative duration (min)			
Median (range)	568.8 (330–837)	547.5 (358–688)	0.606
Anesthesia time (min)			
Median (range)	631.8 (422–905)	608.5 (413–740)	0.471
Amount of blood loss (mL)			
Median (range)	460.3 (0–3880)	382.5 (80–2060)	0.846
Intraoperative fluid balance (mL/kg/h)			
Median (range)	5.71 (2.57–9.98)	6.99 (3.06–11.55)	0.001
Postoperative hospital stay (days) median (range)	23.8 (12–1017)	38.0 (19–217)	< 0.001

ASA American Society of Anesthesiologists, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *Ae* abdominal esophagus, *EGJ* esophagogastric junction, *D2* extended, *D3* super-extended, *VATS* video-assisted thoracoscopic surgery, *HALS* hand-assisted laparoscopic surgery, *NACT* neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy

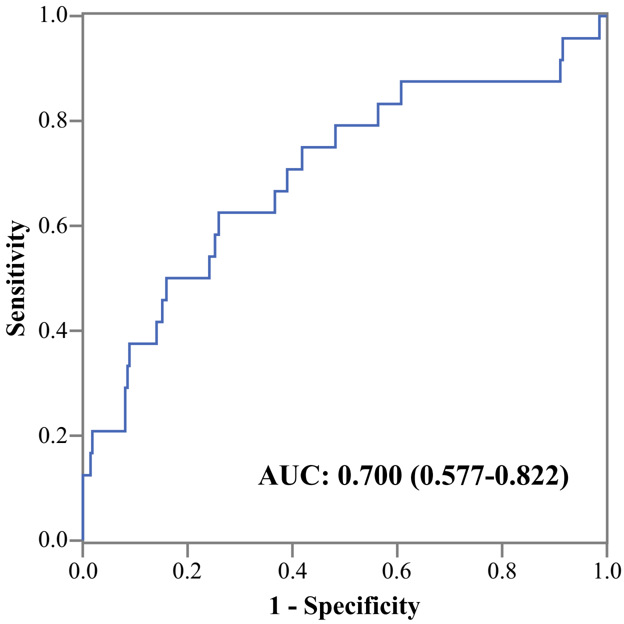

FIG. 1 Receiver operating characteristic curves of lymphorrhea. Area under the curve was 0.700 (95% CI 0.577–0.822; sensitivity 62.5%; specificity 74.1%; cutoff value 6.55, $p = 0.001$)

suggesting a definite effect of radiation on the incidence of chylothorax. Gupta et al.[18] had already reported that post NACRT patients of squamous cell carcinoma of middle third of thoracic esophagus have difficult mediastinal dissection and high chances of developing postoperative chylothorax. In this report, it is suspected that the radiation activates various cellular signaling pathways and leads it difficult to separate esophagus from the surrounding mediastinal structures. This simply means that post-chemoradiotherapy increases the risk of intraoperative injury of TD. However, this type of chylothorax could be avoided by resecting TD or ligating it above the diaphragm. We think there is another pattern of increasing risk after chemoradiotherapy. One adverse effect of radiation is damage to the lymphatic system.[19] Preoperative radiation to the mediastinum might have damaged the local lymphatic system and consequently delayed healing of stumps of small lymphatic vessels caused by lymphadenectomy in the affected region, thereby causing chylothorax.

Lymphatic vessels and TD play a vital role in lipid transport from the intestine to the circulation and in reabsorption and subsequent return of interstitial fluid and fluid leaked into the third space to the venous system.[20,21] Excess perioperative fluid accumulation results in elevation of interstitial fluid volume and consequent increase in the pressure inside the lymphatic vessels. TD will make these leak-prone, and the slight damage during esophagectomy may result in chylothorax. Thus, it is likely that intraoperative fluid imbalance (toward excess) is a risk factor for chylothorax. ROC curve analysis showed an AUC of 0.700 (95% CI 0.577–0.822), sensitivity of 62.5%, specificity of 74.1%, and cutoff value of 6.55. Intraoperative infusion at a rate of 6–12 mL/kg/h was previously recommended.[21,22] However, fluid management at a lower rate (≤ 6.55 mL/kg/h) may be beneficial in preventing chylothorax, because intraoperative fluid imbalance is a potential risk factor. We were able to prove these results even in the validation study.

Our results suggest that TD resection increases the risk of chylothorax compared with TD preservation. Of 24 patients with chylothorax, only 3 had TD preservation, and the remaining 21 underwent TD resection. TD ligation is an established procedure in treating chylothorax, and the report by Crucitti et al.[23] showing the efficacy of TD ligation, is valuable. However, this report focused on the efficacy of TD ligation as a prophylaxis, and TD resection was not performed. We perform TD resection as a part of lymphadenectomy in the majority of our cases ligating TD just above the diaphragm. This ligation is a necessary procedure combined with TD resection and is different from the prophylactic TD ligation without its resection. When the main duct is ligated above the diaphragm, chylothorax may not occur even if the main duct is preserved but injured. However prophylactically ligating TD would not accomplish our goal of TD preservation, i.e., sustaining the postoperative circulating plasma volume. Therefore, we do not ligate TD when it is preserved. When there is neither injury nor stenosis to the duct, we usually do not experience chylothorax even without ligation of TD. In our study, the incidence of chylothorax was rare among patients with preserved TD. We preserve TD in mainly T1 tumors without suspected cancer invasion to the surrounding tissues. By carefully selecting the patients, TD is safely preserved without injuring nor being stenosed. Thus, chylothorax would not become an issue without ligating TD. When there is a suspected injury or stenosis of the duct, ligating TD could be effective for prophylaxis of chylothorax, as Crucitti et al. demonstrated. However, we resected TDs in these cases, and our analysis showed that the rates of chylothorax was higher in the resected patients compared to preserved patients, which is not contradicting to previous reports. Generally, it is thought that the cause of the postoperative chylothorax after resection of TD is looseness of the ligation and dropout of the clip. However, there are some cases in which chylothorax do not improve even when the upper course of TD or visible leaking point is ligated. In most cases, TD is a single duct and passes cephalad into the thorax on the right side of the descending aorta and crosses over the vertebra to the left side at about the level of the fifth thoracic vertebra and flows into the venous systems at the left venous angle. Also, many patterns of variation have been noted, and ligation of a single

TABLE 2 Results of multivariate analysis of the factors predictive of postoperative lymphorrhea

	p value	HR	95% CI
NACRT	0.009	3.430	1.364–8.625
High intraoperative fluid balance (mL/kg/h)	0.001	1.569	1.207–2.039
Thoracic duct resection	0.062	3.389	0.941–12.201

CI confidence interval, *HR* hazard ratio, *NACRT* neoadjuvant chemoradiotherapy

thick lymphatic vessel above the diaphragm may be insufficient to prevent postoperative chylothorax.[24,25] Even if such variation is not present, lymphatics have multiple network formations from the abdominal cavity to the thoracic cavity other than the main stream. Therefore, it should be impossible to ligate all of the lymphatic vessels flowing into the mediastinum. It is true that magnified view is available with VATS, but not with open surgery. Thus, an injury of the main TD would be immediately detected and treated by VATS. However, even with VATS, it is difficult to examine the entire network consisting of many fine ($\leq$1 mm) lymphatic vessels. Furthermore, even if leakage from a small lymphatic vessel is found and sealed with a sealing device, postoperative increase in the pressure inside the lymphatic vessels may result in re-rupture of small lymphatic vessels. This may explain the absence of statistically significant differences between VATS and open surgery in this study. However, because of this study, we have pursued more precise intraoperative observations. This has allowed us to detect and clip rather-thick lymphatic vessels flowing into TD just cephalad to the inferior border, giving us an impression of less frequency of postoperative chylothorax.

Naturally, we consider the cause of typical severe chylothorax to be intraoperative injury of the main TD or rupture of TD at the upper stream of the ligation point. However, milder chylothorax can occur without such major leakage from TD, and the three factors detected in this study may be causative factors. From these results, first, infusion volume will be reduced with the assistance of anesthesiologists so that intraoperative fluid balance becomes < 6.55 mL/kg/h. If intraoperative fluid balance is high after TD resection or chemoradiotherapy, postoperative infusion volume will be reduced, and enteral nutrients will be changed to reduce the pressure inside TD as much as possible. In our hospital, an oligomeric enteral formula is generally administered from postoperative day 2 in all patients. However, given that this is a fat-containing formula, a low-fat formula is used as an alternative in the above patients.

The major limitations of our study were its single-center, retrospective design and the small number of patients examined. However, the current data are from a prospectively constructed database of consecutive patients over a relatively short period of time. A multicenter study with a larger number of cases is warranted.

CONCLUSIONS

This study revealed that post-chemoradiotherapy and high intraoperative fluid balance are predictors of chylothorax after esophagectomy. Additionally, resection of TD may be a predictor of chylothorax. The elucidation of clinicopathological factors that can predict the incidence of chylothorax will help to establish more effective perioperative management for esophageal cancer patients.

AUTHOR CONTRIBUTIONS Yu Ohkura, Masaki Ueno, and Junichi Shindoh designed the study, wrote the manuscript, revised it critically for important intellectual content, and gave final approval for the content; Yu Ohkura, Masaki Ueno, Masaki Ueno, Toshiro Iizuka, Hairin Ka and Harushi Udagawa created study materials or recruited patients.

CONFLICT OF INTEREST The authors declare that they have no conflict of interest.

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