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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Effect of Resection of the Thoracic Duct and Surrounding Lymph Nodes on Short- and Long-Term and Nutritional Outcomes After Esophagectomy for Esophageal Cancer

Naoya Yoshida, MD, PhD[1,2], Yohei Nagai, MD, PhD[1], Yoshifumi Baba, MD, PhD[1], Yuji Miyamoto, MD, PhD[1], Shiro Iwagami, MD, PhD[1], Masaaki Iwatsuki, MD, PhD[1], Yukiharu Hiyoshi, MD, PhD[1], Kojiro Eto, MD, PhD[1], Takatsugu Ishimoto, MD, PhD[1,2], Yuki Kiyozumi, MD, PhD[1], Daichi Nomoto, MD[1], Takahiko Akiyama, MD[1], Yu Imamura, MD, PhD[3], Masayuki Watanabe, MD, PhD[3], and Hideo Baba, MD, PhD[1]

[1]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [2]Division of Translational Research and Advanced Treatment Against Gastrointestinal Cancer, Kumamoto University, Kumamoto, Japan; [3]Department of Gastroenterological Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan

ABSTRACT

Background. The effect of resection of the thoracic duct (TD) along with surrounding lymph nodes (LN) on short- and long-term outcomes of esophagectomy in esophageal cancer patients is not well defined.

Methods. A total of 537 consecutive patients suffering from esophageal cancer who underwent three-incision esophagectomy between April 2005 and August 2018 were eligible for short-term outcome analysis. Among them, 487 patients who underwent surgery before August 2017 were eligible for analysis of long-term outcomes. Moreover, 164 patients who underwent esophagectomy after August 2012 and had no recurrence at 1-year postoperative follow-up were prospectively investigated for postoperative nutritional status.

Results. A total of 145 patients (27.0%) underwent TD resection with surrounding LN. Since the clinical stage was significantly more advanced in the removal group, preoperative treatment was more frequently performed in them. The operative time was significantly longer in the removal group. Intraoperative bleeding was higher in the removal group. Morbidity of Clavien–Dindo classification (CDc) $\geq$ II and pulmonary morbidities were frequently observed in the removal group. Multivariate analysis suggested that TD resection was an independent risk factor for pulmonary morbidities. Moreover, it may be associated with the incidence of CDc $\geq$ II morbidity. Greater numbers of LN were dissected in the thorax of patients in the removal group. However, overall survival was equivalent irrespective of the TD procedure in each stage. Nutritional status at 1-year follow-up was equivalent between the groups.

Conclusions. On the basis of the present results, routine removal of the TD during esophagectomy is not recommended.

A recent study using fresh-frozen human cadavers reported that thoracic duct lymph nodes (TDLN) exist within the fatty tissue surrounding the thoracic duct (TD), and may be regional lymph nodes (LN) for thoracic esophageal cancer.[1] Resection of the TD with surrounding LN is sometimes performed during esophagectomy aiming for complete lymphadenectomy. However, whether TD resection can contribute to improving survival outcomes has not been well established.

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H. Baba, MD, PhD
e-mail: hdobaba@kumamoto-u.ac.jp

The influence of TD resection on short-term outcomes after esophagectomy has also seldom been explored. Two previous studies with a small cohort and one case report suggested that it can be a cause of several unfavorable complications.[2–4] In addition, removal of the TD may create a nutritional disadvantage in the early postoperative period.[5] However, it is unclear whether TD resection adversely affects nutritional status in the long term after esophagectomy. It is important to investigate the effect of TD resection on clinical course to establish its clinical value for esophagectomy.

Thus, this study aimed to clarify the effect of TD resection (with surrounding LN) on short- and long-term outcomes and nutritional status at 1 year post-esophagectomy.

METHODS

Patients

Short- and long-term outcomes and postoperative nutritional status according to TD resection were analyzed using different cohorts (Fig. 1). A total of 655 patients underwent three-incision esophagectomy for esophageal cancer at Kumamoto University Hospital between April 2005 and August 2018. Patients who underwent two-stage esophagectomy (19), salvage esophagectomy after definitive chemoradiotherapy (38), and ligation only for intraoperative TD injury (9) were excluded. Patients with distant metastasis (excluding supraclavicular LN) (14) and uncertain data on the TD resection (48) were also excluded. Consequently, 537 patients were analyzed for short-term outcomes. Of them, 487 who underwent surgery before August 2017 were investigated for long-term outcomes. In addition, 164 patients who underwent esophagectomy after August 2012 and had no recurrence at 1-year postoperative follow-up were prospectively investigated for postoperative nutritional status. The study procedures were approved by our facility's institutional review board (registry number 1655).

Treatment Strategy

The details of our treatment strategy are available elsewhere.[6] Neoadjuvant chemotherapy has been administered to patients with non-T4 node-positive tumors since August 2008. Neoadjuvant chemoradiotherapy (CRT) was commonly administered to patients with T4 tumors. The pretreatment clinical stage was classified in accordance with the Cancer Staging Manual version 7.[7]

Esophagectomy

Esophagectomy in this study was defined as a three-incision (neck, chest, and abdomen) esophagectomy with two- or three-field lymphadenectomy. Chest manipulation was conducted from the right thorax. Minimally invasive esophagectomy (MIE) was started in May 2011.

Treatment Strategy for TD

We principally removed TD when the primary tumor was suspected to invade it. We also removed it when mediastinal LN metastasis existed around and along the

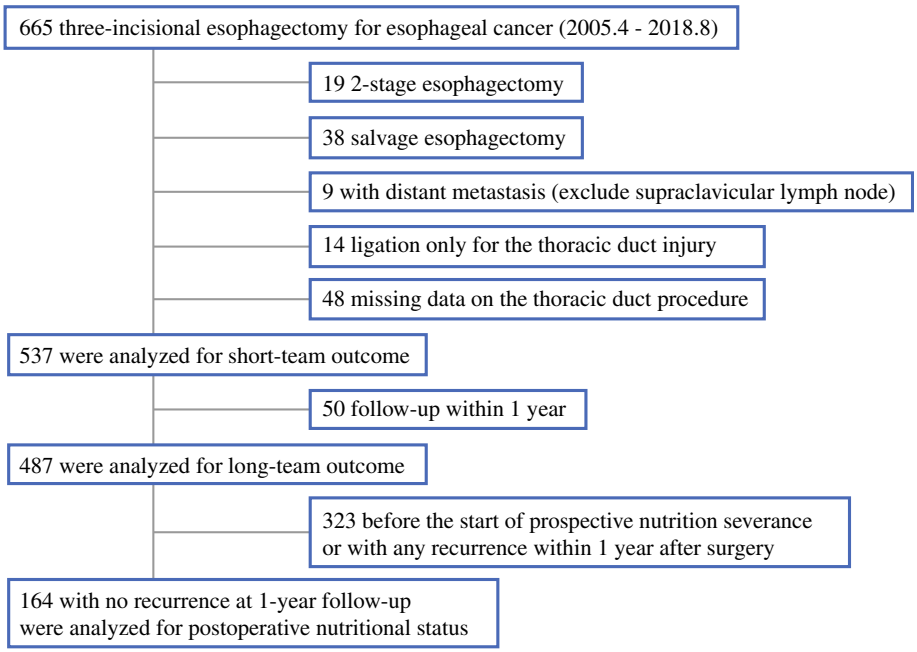

FIG. 1 Flow chart of analyzed patients

TD. Most cases of LN metastasis were determined via a preoperative examination and the surgeon's impression during surgery. TD resection was performed with the LN around it. Cases of TD removal alone and ligation only for the intraoperative injury were excluded from this study.

Definition of Morbidities

Definitions of morbidities proposed by the Society of Thoracic Surgeons General Thoracic Surgery were adopted for this study.[8] The details of the morbidities are available elsewhere.[9] A morbidity constituted any condition with Clavien–Dindo classification (CDc) $\geq$ II.[10]

Follow-Up Evaluation

The patients were followed up at 1–3-month intervals at least for 5 years or until death. Prospective nutrition severance at 1-year postoperative follow-up was started in August 2013 for patients without recurrence at that time. Overall survival was defined as the interval between date of esophagectomy and date of death.

Statistical Methods

Statistical analysis was performed using the software package StatView^{TM} version 5.0 (Abacus Concepts, Inc., Berkeley, CA, USA). The Chi square test was used for intergroup comparisons. Fisher's exact test was used when any cell in the matrix had fewer than five cases. The Mann–Whitney *U* test or Student's *t* test was used to compare unpaired samples. Survival analysis was performed using the Kaplan–Meier method according to clinical stage. Survival time distribution was assessed using the log-rank test. Probability level < 0.05 was considered statistically significant.

RESULTS

Patient Background

Patient characteristics are listed in Table 1 according to TD surgical procedure. A total of 145 patients (27.0%) underwent TD resection with TDLN dissection. The mean age of patients who underwent removal was significantly lower, and the clinical stage in the removal group was significantly more advanced. Thus, preoperative treatment was frequently performed. Open esophagectomy was frequently conducted in the removal group.

Short-Term Outcomes After Surgery

Table 2 presents the short-term outcomes after esophagectomy. Operative time was significantly longer in the removal group regardless of thoracic procedure. Intraoperative bleeding was greater in the removal group in patients treated with MIE. The crude data of postoperative morbidities suggested that any morbidity of CDc $\geq$ II, pneumonia, any pulmonary morbidity, and anastomotic leakage were frequently observed in the removal group. CRT can adversely affect the incidence of postoperative morbidities after esophagectomy;[11,12] thus, short-term outcomes of cases without preoperative CRT were analyzed separately. Consequently, any morbidity of CDc $\geq$ II and any pulmonary morbidity also significantly occurred in the removal group.

To strengthen the current results, we conducted a multivariate analysis on the incidence of any morbidity of CDc $\geq$ II and any pulmonary morbidity (Table 3). Consequently, TD resection was an independent risk factor for any pulmonary morbidity [hazard ratio (HR) for morbidity in patients with TD preservation = 0.43; 95% confidence interval (CI) 0.253–0.730, $P = 0.002$]. In addition, TD resection might be associated with the incidence of any morbidity of CDc $\geq$ II (HR for morbidity in patients with TD preservation = 0.68; 95% CI 0.455–1.003, $P = 0.052$).

Number of LN Dissected in the Thorax

Significantly greater numbers of LN in the thorax were dissected in the removal group (Supplemental Table 1).

Long-Term Outcome After Surgery

Figure 2 depicts Kaplan–Meier curves of overall survival between the removal and preserve groups according to clinical stage. Overall survival was statistically equivalent irrespective of the TD procedure in all stages.

Nutritional Status After Surgery

Table 4 presents nutritional parameters at 1-year postoperative follow-up in patients with no recurrence. Weight and body mass index (BMI) changes, serum albumin, hemoglobin, and total lymphocyte count 1 year after surgery were equivalent irrespective of TD procedure.

DISCUSSION

In this study, we obtained several interesting results regarding the value of TD resection during esophagectomy. First, TD removal deteriorated short-term outcomes after

TABLE 1 Characteristics of patients according to the thoracic duct procedure

Variable		Thoracic duct		*P*
		Removal (*N* = 145)	Preserve (*N* = 392)	
Age	Years	64.4 ± 7.8	66.9 ± 8.2	0.002
Sex	Male:female	130:15	340:52	0.363
BMI	< 18.5:18.5–24.9:≥ 25 kg/m^2	20:106:19	46:281:65	0.545
Brinkman index	< 800:≥ 800	75:69[a]	210:181[a]	0.738
Performance status	0:1:2	130:13:2	342:46:4	0.628
Comorbidity				
Diabetes mellitus	Present:absent	17:128	84:308	0.011
Respiratory comorbidity	Present:absent	44:101	138:254	0.291
Cardiovascular comorbidity	Present:absent	67:78	209:183	0.143
Tumor location	Ce:Ut:Mt:Lt:Ae	0:25:86:29:5	2:51:199:128:12	0.052
Clinical stage	I:II:III:IV[b]	25:24:83:13	212:74:93:13	< 0.001
Preoperative treatment	None:NAC:NACRT	39:80:26	265:97:30	< 0.001
Surgery				
Thoracic approach	Open:thoracoscopic	108:37	175:217	< 0.001
Type of conduit	Stomach:colon:others	134:11:0	368:22:2	0.488

Data expressed as number of cases or mean number ± standard deviation

BMI body mass index, *Ce* cervical esophagus, *Ut* upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic, *Ae* abdominal esophagus, *NAC* neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy

[a]One missing datum

[b]Cases only due to supraclavicular lymph node metastasis

TABLE 2 Short-term outcomes after esophagectomy

Variable	All cases			Cases without preoperative CRT		
	Thoracic duct		*P*	Thoracic duct		*P*
	Removal (*N* = 145)	Preserve (*N* = 392)		Removal (*N* = 119)	Preserve (*N* = 362)	
Operative time, OE (min)	548 ± 11	500 ± 8	0.005	546 ± 122	503 ± 106	0.019
Operative time, MIE (min)	605 ± 17	582 ± 6	0.045	600 ± 105	583 ± 92	0.125
Bleeding, OE (g)	487 ± 86	480 ± 32	0.191	491 ± 107	480 ± 34	0.272
Bleeding, MIE (g)	349 ± 63	169 ± 23	0.002	350 ± 64	266 ± 24	0.002
Any morbidity of CDc ≥ II	63 (43.4)	133 (33.9)	0.042	53 (44.5)	121 (33.4)	0.029
Severe morbidity of CDc ≥ IIIb	22 (15.2)	38 (9.7)	0.074	16 (13.4)	34 (9.4)	0.209
Pneumonia	21 (14.5)	33 (8.4)	0.038	17 (14.3)	31 (8.6)	0.071
Any pulmonary morbidity	39 (26.9)	48 (12.2)	< 0.001	33 (27.7)	45 (12.4)	< 0.001
Surgical-site infection (leak included)	40 (27.6)	94 (24.0)	0.391	35 (29.4)	89 (24.6)	0.296
Anastomotic leakage	12 (8.3)	58 (14.8)	0.046	10 (8.4)	56 (15.5)	0.052
Cardiovascular morbidity	6 (4.1)	28 (7.1)	0.204	4 (3.4)	22 (6.1)	0.351
Chylothorax	3 (2.1)	5 (1.3)	0.451	2 (1.7)	5 (1.4)	0.685
Reoperation	10 (7.9)	25 (6.4)	0.829	9 (7.6)	23 (6.4)	0.646
In-hospital mortality	1 (0.7)	1 (0.3)	0.468	1 (0.8)	1 (0.3)	0.434
Hospital stay (days)	26 ± 1.6	23 ± 1.0	0.421	25 ± 1.0	23 ± 1.7	0.458

Data expressed as number (%) of cases or median number ± standard error

CRT chemoradiotherapy, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *CDc* Clavien–Dindo classification

TABLE 3 Multivariate analysis for factors associated with postoperative complications

Variable	Factor	Objective variable	Control	Univariate analysis		Multivariate analysis	
				HR (95% CI)	*P*	HR (95% CI)	*P*
Any morbidity of CDc ≥ II	Sex	Male	Female	1.81 (1.012–3.234)	0.046	1.49 (0.818–2.717)	0.192
	Brinkman index	≥ 800	< 800	1.49 (1.049–2.128)	0.026	1.38 (0.957–1.992)	0.084
	Conduit	Gastric tube	Others	0.36 (0.177–0.719)	0.004	0.39 (0.193–0.798)	0.010
	Thoracic duct	Preserve	Removal	0.67 (0.453–0.987)	0.043	0.68 (0.455–1.003)	0.052
Any pulmonary morbidity	Sex	Male	Female	2.62 (1.022–6.721)	0.045	2.26 (0.858–5.953)	0.099
	Brinkman index	≥ 800	< 800	1.68 (1.053–2.665)	0.029	1.53 (0.946–2.473)	0.083
	Clinical stage	I, II	III, IV	0.59 (0.372–0.939)	0.026	0.92 (0.476–1.782)	0.806
	Preoperative treatment	Present	Absent	1.76 (1.110–2.799)	0.016	1.26 (0.651–2.439)	0.493
	Thoracic duct	Preserve	Removal	0.38 (0.236–0.610)	< 0.001	0.43 (0.253–0.730)	0.002

HR hazard ratio, *CI* confidence interval, *CDc* Clavien–Dindo classification

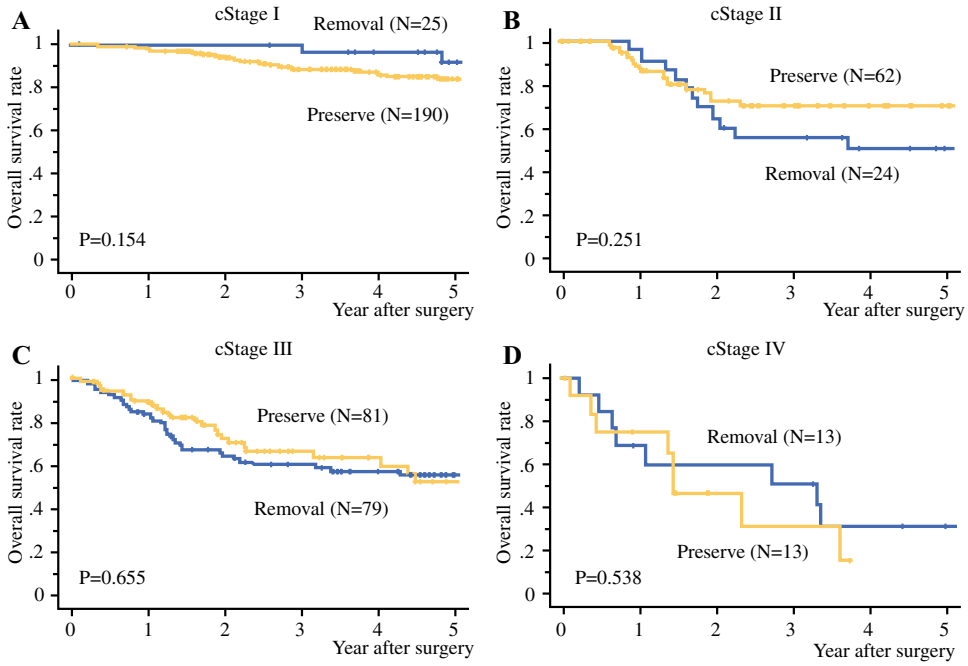

FIG. 2 Kaplan–Meier curves of overall survival according to thoracic duct treatment: **a** cStage I, **b** cStage II, **c** cStage III, and **d** cStage I

esophagectomy. Notably, operative time, intraoperative bleeding, and the incidence of postoperative morbidity may change for the worse upon TD removal. Second, TD removal increased the number of LN to be dissected in the thorax. However, it did not contribute to improved survival outcomes after esophagectomy. Third, TD removal did not adversely affect postoperative nutritional status at 1 year post-esophagectomy.

Surprisingly, the effect of TD resection on short-term outcomes after esophagectomy has seldom been reported. To date, only two studies with small cohorts and one case report have been published.[2,4] Anand et al.[2] compared immediate postoperative hemodynamic parameters in 10 patients with TD resection with those of 12 patients without TD resection during MIE. They concluded that TD resection can be a cause of hemodynamic changes and increases in pulse rate in the immediate postoperative period. Imamura et al.[3] compared postoperative fluid balance of 22 patients with TD resection with that of 15 patients without resection and concluded that more fluid was necessary during surgery and the postoperative 24 h for patients who underwent TD resection. They also reported a case of postoperative uncontrollable ascites after TD resection in a patient with chronic hepatitis who finally died of peritonitis and renal failure during the hospital stay. The present study suggests that TD removal can be

TABLE 4 Nutritional status 1 year after surgery in patients with no recurrence

Variable	Thoracic duct		*P*
	Removal (*N* = 29)	Preserve (*N* = 135)	
Weight change (ΔBW/preoperative BW) (%)	− 11.1 ± 9.3	− 10.5 ± 8.1	0.700
BMI change (ΔBMI/preoperative BMI) (%)	− 10.9 ± 9.1	− 10.2 ± 8.3	0.680
Albumin			
Preoperative (g/dL)	3.9 ± 0.4	4.0 ± 0.4	0.946
1 year after surgery (g/dL)	4.1 ± 0.4	4.0 ± 0.4[a]	0.123
Hemoglobin			
Preoperative (g/dL)	12.5 ± 1.5	13.0 ± 1.8	0.142
1 year after surgery (g/dL)	12.9 ± 1.3	12.6 ± 1.4[a]	0.261
Total lymphocyte count			
Preoperative (/mL)	1540 ± 560	1650 ± 590[a]	0.337
1 year after surgery (/mL)	1600 ± 690	1520 ± 530[a]	0.477

Data expressed as mean number ± standard deviation

BW body weight, *BMI* body mass index

[a]One missing datum

associated with increased operative time, intraoperative bleeding, and postoperative morbidities. Although several studies have shown that prophylactic TD resection is useful for preventing postoperative chylothorax after esophagectomy,[13,14] the incidence of chylothorax was statistically equivalent between the removal and preserve groups in this study. The intergroup differences in patient backgrounds may have affected the present worse short-term outcomes of the removal group. Several metaanalyses that investigated the short-term outcomes of esophagectomy after neoadjuvant CRT suggested that preoperative CRT increases postoperative mortality in patients with esophageal squamous cell carcinoma.[11,12] Thus, we separately investigated the short-term outcomes in patients without preoperative CRT. However, short-term outcomes of patients without preoperative CRT were also worse in the removal group. In addition, multivariate analysis suggested that TD resection was an independent risk factor for pulmonary morbidities. Regarding short-term outcomes, unnecessary resection of TD should not be conducted during esophagectomy.

TD resection did not contribute to improving long-term outcomes after esophagectomy, although the number of dissected LN in the thorax significantly increased. Matsuda et al.[15] reported a similar result regarding the number of resected TDLN and survival outcomes after TD resection These results may imply that TDLN surrounding the TD are not regional LN for thoracic esophageal cancer. Metastasis to the TDLN may correspond to cM1 stage (or cN4 stage in the 11th Japanese Classification of Esophageal Cancer). On the other hand, Matsuda et al. also suggested that recurrence-free survival of cStage I patients tended to increase in patients who underwent TD resection ($P = 0.055$). In the current study, the overall survival of patients in the removal group with cStage I esophageal cancer was also better than that in the preserve group but without significance ($P = 0.154$). Prophylactic dissection of TDLN is possibly useful in cStage I esophageal cancer.

We discuss herein why removal of the TD with TDLN may be effective to improve the survival outcome in cStage I esophageal cancer. A randomized controlled trial (RCT) was previously conducted to elucidate whether D2 lymphadenectomy plus paraaortic nodal dissection (PAND) can contribute to improving the survival outcome of patients with gastric cancer.[16] In the subgroup analysis of the study, survival was better only in patients with pathologically negative nodes when D2 lymphadenectomy plus PAND was conducted. On the other hand, in patients with LN metastasis, the survival after D2 lymphadenectomy plus PAND was worse. This result may imply that wide LN dissection is effective in patients with early-stage cancer. Cancer generally progresses from a local disease to a systemic disease. Surgery with LN dissection is generally effective in early-stage cancers. Once the cancer has advanced systemically, the usefulness of local treatments such as surgery and radiation decreases. Resection of the TD with the surrounding LNs possibly corresponds to wide LN dissection. It may contribute to better survival in patients with early-stage esophageal cancer by eradicating macro- and micro-LN metastases. However, once esophageal cancer has advanced to cStage II, III, and IV, wide LN dissection with TD resection may not be useful in improving the prognostic outcome. In addition, surgery with wide LN dissection is associated with frequent postoperative morbidities, which can result in worse survival outcomes.[17] The above-mentioned RCT also reported more

frequent complications in the D2 lymphadenectomy plus PAND group than in the D2 lymphadenectomy alone group. Patients with advanced esophageal cancer often have nutritional and hematological disadvantages owing to swallowing difficulty and invasive preoperative treatment. TD resection in patients with advanced esophageal cancer may pose excessive burden on the patient, which can result in frequent postoperative morbidities and worse prognosis. Further prospective investigations in larger cohorts are necessary to elucidate the real prognostic value of TD removal with TDLN dissection in cases of early-stage esophageal cancer.

Lymph fluid in TD is full of lipids and contains small amounts of protein. We projected that TD removal may adversely affect nutritional status at 1 year post-esophagectomy. However, in the current study, changes in body weight and BMI, albumin and hemoglobin levels, and total lymphocyte counts were equivalent between the removal and preserved groups. There has been only one randomized study to date that has examined the association of TD procedure with postoperative nutritional status using a small sample cohort.[5] In that study, Aiko et al. suggested that patients who underwent TD ligation did not benefit from immediate postoperative enteral nutrition. TD blockade may be associated with immediate retention of lymphatic flow, postoperative hemodynamic changes, and subsequent poor nutritional condition in the early postoperative period. However, at 1 year post-operation, another route of lymphatic flow may have been reconstructed,[3] which may have resulted in the nutritional stability noted in this study. In addition, various factors correlate with nutritional status after esophagectomy. A previous study suggested that a pyloroplasty can prevent postoperative weight loss after esophagectomy.[18] Yamasaki et al.[19] documented that reconstruction route significantly affects post-esophagectomy weight loss. The impact of TD resection on postoperative nutritional status may be slight compared with that of other surgical procedures following the early postoperative period.

On the basis of the present results, routine TD resection with TDLN dissection is not recommended. We considered that removal of the TD is necessary only when the primary tumor is suspected to be invading the TD or in the presence of metastatic LNs. In addition, as mentioned above, prophylactic dissection of TDLNs is possibly useful in cStage I esophageal cancer.

This study has several limitations. First, it was retrospective and performed at a single institute. Second, the indications for TD resection were not rigidly determined. Patient backgrounds differed between groups in terms of clinical stage, preoperative treatment, and surgical approach in the thorax. Thus, we analyzed long-term outcomes in accordance with cStage. However, the short-term outcomes may be affected by the abovementioned differences, although we separately analyzed patients who had undergone no preoperative treatment or preoperative chemotherapy. Finally, the length of our observation period (from 2005 to 2018) could be a cause of historical bias with regard to treatment strategy, operational method, and perioperative management.

CONCLUSIONS

We believe that routine TD resection with TDLN dissection during esophagectomy for esophageal cancer is not recommended from the perspective of short- or long-term outcomes in this study. We assume that a future prospective randomized study will be necessary to verify the authentic value of TD resection during esophagectomy.

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