



# Thoracic Duct Resection During Esophagectomy Does Not Contribute to Improved Prognosis in Esophageal Squamous Cell Carcinoma: A Propensity Score Matched-Cohort Study

Oshikiri, Taro ; Takiguchi, Gousuke ; Miura, Susumu ; Gotou, Hironobu ; Otsubo, Dai ; Hasegawa, Hiroshi ; Yamamoto, Masashi ; Kanaji, Shingo ; ...

**(Citation)**

Annals of Surgical Oncology, 26(12):4053-4061

**(Issue Date)**

2019-07-16

**(Resource Type)**

journal article

**(Version)**

Accepted Manuscript

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**(URL)**

<https://hdl.handle.net/20.500.14094/0100477306>



**Authors and their affiliations:** Taro Oshikiri, MD<sup>1</sup>, Gosuke Takiguchi, MD<sup>1</sup>, Susumu Miura, MD<sup>1</sup>, Hironobu Goto, MD<sup>2</sup>, Dai Otsubo, MD<sup>2</sup>, Hiroshi Hasegawa, MD<sup>1</sup>, Masashi Yamamoto, MD<sup>1</sup>, Shingo Kanaji, MD<sup>1</sup>, Kimihiro Yamashita, MD<sup>1</sup>, Takeru Matsuda, MD<sup>3</sup>, Yasuhiro Fujino, MD<sup>2</sup>, Masahiro Tominaga, MD<sup>2</sup>, Tetsu Nakamura, MD<sup>1</sup>, Satoshi Suzuki, MD<sup>4</sup>, and Yoshihiro Kakeji, MD<sup>1</sup>

1. Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan
2. Department of Gastroenterological Surgery, Hyogo Cancer Center, 13-70, kitaoji-cho, Akashi, Hyogo, 673-8558, Japan
3. Division of Minimally Invasive Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan
4. Department of Social Community Medicine and Health Science, Division of Community Medicine and Medical Network, Graduate School of Medicine, Kobe University, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan

**Address correspondence and reprint requests to:**

Taro Oshikiri, MD

Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan

Telephone: 81-78-382-5925

Fax: 81-78-382-5939 E-mail: [oshikiri@med.kobe-u.ac.jp](mailto:oshikiri@med.kobe-u.ac.jp)

**Manuscript Title:**

Thoracic duct resection during esophagectomy does not contribute to improved prognosis in esophageal squamous cell carcinoma. A propensity score matched-cohort study

**Running head:** Thoracic duct resection during esophagectomy

**Conflicts of interest:** Taro Oshikiri, Gosuke Takiguchi, Susumu Miura, Hironobu Goto, Dai Otsubo, Hiroshi Hasegawa, Masashi Yamamoto , Shingo Kanaji, Kimihiro Yamashita, Takeru Matsuda, Yasuhiro Fujino, Masahiro Tominaga, Tetsu Nakamura, Satoshi Suzuki, and Yoshihiro Kakeji have no conflicts of interest or financial ties to disclose.

**Synopsis:**

In esophagectomy for esophageal squamous cell carcinoma (ESCC), thoracic duct (TD) resection to dissect lymph nodes around the TD does not contribute to improved survival but increases complications. Prophylactic TD resection should be avoided in esophagectomy for ESCC.

## **Abstract**

### **Purpose**

Esophagectomy with extended lymphadenectomy remains the mainstay of treatment for localized esophageal squamous cell carcinoma (ESCC). Thoracic duct (TD) resection has been recommended as part of extended lymphadenectomy although its merits are unclear. The aim of this multi-institutional, matched-cohort study is to clarify whether TD resection improves prognosis in esophagectomy for ESCC.

### **Methods**

In this multi-institutional, matched-cohort study of 399 patients with ESCC who underwent McKeown esophagectomy between 2010 and 2014, the primary outcomes were overall survival (OS), disease-free survival (DFS), and cause-specific survival (CSS). Secondary outcomes were perioperative results and recurrence patterns.

### **Results**

Based on a propensity score, 122 TD-resected or 122 TD-preserved patients in all stages were selected (median follow-up, 4.5 years). The 5-year OS, DFS, and CSS rates in the TD-resected versus TD-preserved groups were 49% versus 60%, 53% versus 57%, and 58% versus 70%, respectively, without any significant differences. Operative time for the thoracic procedure was significantly longer and the number of retrieved mediastinal nodes was significantly higher in the TD-resected group ( $P=0.009$  and  $0.005$ , respectively). The rates of chylothorax and left recurrent laryngeal nerve (RLN) palsy were significantly higher in the TD-resected group ( $P=0.041$  and  $0.018$ , respectively). There were no significant differences in rates of local and distant metastases between the

two groups.

### **Conclusion**

TD resection does not contribute to improve OS, DFS, and CSS in ESCC but increases the incidence of chylothorax and left RLN palsy. Prophylactic TD resection should be avoided in esophagectomy for ESCC.

Key words: esophageal squamous cell carcinoma, McKeown esophagectomy, thoracic duct

## **Introduction**

The world's first case of transthoracic esophagectomy was reported by Torek in 1913.<sup>1</sup> Since then, esophagectomy with extended lymphadenectomy has remained the mainstay of treatment for localized esophageal squamous cell carcinoma (ESCC).<sup>2-4</sup> As a part of extended lymphadenectomy, thoracic duct (TD) resection has been recommended because there are some mediastinal lymph nodes (LNs) in the adipose tissue surrounding the TD (TDLNs).<sup>5</sup> Indeed, an increased number of dissected TDLNs with TD resection and TDLNs metastasis in advanced disease have been reported.<sup>6</sup> On the other hand, TD resection was reported to cause intravenous volume loss, hemodynamic disturbances, and delay enteral feeding after surgery.<sup>7,8</sup>

TD resection in esophagectomy still remains controversial because there has been no study to investigate the oncological outcomes of esophagectomy for ESCC with TD resection. If there is no advantage in prognosis, TD resection that causes hemodynamic disturbances should be avoided. In this study, we hypothesized that TD resection in esophagectomy with extended lymphadenectomy does not contribute to improved prognosis but increases postoperative complications. Thus, we planned a large retrospective cohort study of esophagectomy with TD resection and preservation for ESCC with propensity score matching.

## **Methods**

### **Patients**

This was a multi-institutional, propensity score matched-cohort study of patients with ESCC who underwent Mckeown esophagectomy<sup>9</sup> at Kobe University and Hyogo Cancer Center between 2010 and 2014. All patients were staged preoperatively with

endoscopy and enhanced computed tomography (CT). The diagnosis of esophageal cancer was based on the seventh edition of the Union for International Cancer Control tumor node metastasis (TNM) cancer staging system.<sup>10</sup> Prior to surgery, two cycles of cisplatin/5-fluorouracil were administered as preoperative chemotherapy to patients with clinical (c)-Stage II/III disease. None of the patients received preoperative chemoradiotherapy. Although there were no surgeon-specific criteria in this study, all the responsible surgeons were required to have enough experience to perform esophagectomy. Furthermore, in this study, thoracoscopic esophagectomy was performed only by surgeons with the Japanese endoscopic surgical skills qualification.<sup>11</sup> Eligibility criteria consisted of: (1) age  $\geq 20$  and  $\leq 80$  years; (2) histologically proven ESCC; (3) cT1–3, cN0–3, cM0 disease; (4) resection of primary ESCC; and (5) no history of primary cancer of other organs. C-stage IA patients and IB–IV patients were selected from all eligible patients and included in subgroup analyses.

#### TD resection criteria and surgical procedure

The two affiliated institutions have a uniform therapeutic strategy. Namely, most TD-resected esophagectomies were performed from 2010 to 2011. Starting in 2011, TD-preserved esophagectomies were mostly performed under the hypothesis that TD resection may not contribute to improved prognosis.

TD and TDLNs were dissected en bloc. Practically, in the middle and lower mediastinal approach, TD and TDLNs were divided from the descending aorta. The TD was then clipped behind the lower thoracic esophagus and resected above the diaphragm.

Finally, the TD was clipped and divided at the level of the thoracic inlet.

#### Postoperative feeding protocols

Liquid elemental diets including few fatty acids were injected into the patients' intestinal tract since postoperative day 2 in both groups.

#### Outcomes

Patient characteristics, preoperative chemotherapy, intraoperative parameters, adverse events, length of hospital stay, and prognosis were retrieved from a database. The primary outcomes were overall survival (OS), disease-free survival (DFS), and cause-specific survival (CSS). Basically, local and distant recurrences were confirmed by CT. Secondary outcomes were operative time, number of retrieved nodes, circumferential resection margin status, chylothorax, pneumonia, leakage, recurrent laryngeal nerve (RLN) palsy, length of hospital stay, and recurrence pattern. For subgroup analyses, survival in c-stage IA patients and IB–IV patients were also estimated. This study was approved by the Institutional Review Board and the Ethics Committee of Kobe University and Hyogo Cancer Center.

#### Definition of Chylothorax

Chylothorax was suspected if there was excessive chest drain output (more than 1000 mL/day) and the color of chest drainage fluid turned milky white after tube feeding or oral ingestion.

## Statistical Analysis

### Propensity score matching

A key issue in any case-control study is the matching of cases to controls. The propensity score is the conditional probability of being assigned to a particular treatment given a vector of observed covariates. Both large-sample and small-sample theory show that adjusting for the scalar propensity score is sufficient to remove bias from all observed covariates.<sup>12</sup> In this retrospective study, we used propensity score matching to assemble two comparable groups. We included depth of tumor invasion, lymph node metastasis, preoperative chemotherapy, and thoracic procedure as covariates. We matched each patient in the TD-resected group sequentially to a patient in the TD-preserved group who had the closest propensity score using simple 1:1 nearest-neighbor matching without replacement. To prevent poor matches, a caliper of 0.20 of the standard deviation of the logit of the propensity score was used.

For subgroup analyses of c-stage IA patients and c-stage IB–IV patients, survival analyses were performed using propensity score matching as described above. Among c-stage IA patients, preoperative chemotherapy and thoracic procedure were used as covariates. Among c-stage IB–IV patients, depth of tumor invasion, lymph node metastasis, preoperative chemotherapy, and thoracic procedure were used as covariates.

Differences in categorical variables between the two groups were analyzed using the  $\chi^2$  test. Continuous variables were analyzed using the Mann-Whitney U test or Student's t-test, as appropriate. Survival curves were estimated using the Kaplan-Meier

method, and compared using the log-rank test. All *P* values less than 0.05 were considered statistically significant. All statistical computations, including propensity score matching, were performed using JMP<sup>®</sup> 11 (SAS Institute, Cary, NC, USA).

## Results

### Patients

A total of 399 patients underwent Mckeown esophagectomy with two-field or three-field lymph node dissection and reconstruction with curative intent at Kobe University and Hyogo Cancer Center between 2010 and 2014. Of these, 339 patients were included in the study. Most of them (314 patients) underwent thoracoscopic esophagectomy. The TD-resected group contained 132 patients and the TD-preserved group contained 207 patients. Patient characteristics are shown in Table 1. Patients were matched into TD-resected and TD-preserved groups of 122 based on the propensity score. Differences in baseline characteristics, depth of tumor invasion, and preoperative chemotherapy were statistically significant before adjusting; however, these differences were all eliminated after propensity score matching (Table 1). The median length of follow-up for censored cases was 5.2 years (range, 1.9–7.9 years).

There were 86 c-stage IA patients included. The TD-resected group contained 25 patients and the TD-preserved group contained 61 patients. Using the propensity score, these patients were matched into TD-resected and TD-preserved groups of 25. Significant differences in baseline characteristics were not observed before and after propensity score matching (data not shown). The median length of follow-up for

censored cases was 5.6 years (range, 2.2–7.9 years).

There were 253 c-stage IB–IV patients included. The TD-resected group contained 107 patients and the TD-preserved group contained 146 patients. Patient characteristics are shown in Table 2. Using the propensity score, these patients were matched into TD-resected and TD-preserved groups of 96 (Table 2). The differences in baseline characteristics and preoperative chemotherapy were statistically significant before adjustment; however, these differences were all eliminated after propensity score matching (Table 2). The median length of follow-up for censored cases was 5.0 years (range, 1.9–7.5 years).

#### Outcomes

Across all stages, the 5-year OS rate was 49% in the TD-resected group versus 60% in the TD-preserved group ( $P=0.08$ ; Fig. 1A). The 5-year DFS rate was 53% in the TD-resected group versus 57% in the TD-preserved group ( $P=0.35$ ; Fig. 1B). The 5-year CSS rate was 58% in the TD-resected group versus 70% in the TD-preserved group ( $P=0.08$ ; Fig. 1C). There was a tendency toward OS and CSS extension in the TD-preserved group that did not reach statistical significance. Operative outcomes were shown in Table 3. Operative time for the thoracic procedure was significantly longer in the TD-resected group ( $P=0.009$ ). The number of retrieved mediastinal nodes was also significantly higher in the TD-resected group ( $P=0.005$ ). There were no significant differences between two groups in circumferential resection margin status.

Regarding postoperative complications, the rates of chylothorax and left RLN

palsy (Clavien-Dindo classification grade  $\geq$ II)<sup>13</sup> were significantly higher in the TD-resected group ( $P=0.041$  and  $0.018$ , respectively). All three patients with chylothorax needed surgical intervention. Postoperative hospital stay was significantly longer in the TD-resected group ( $P=0.045$ ) (Table 3). Postoperative recurrence patterns are shown in Table 4. There were no significant differences in the location of recurrence: mediastinum, area around the TD, local (area near the primary tumor), and distant metastases between the two groups. The “area around the TD” means the TD component in the TD-preserved group or the place where the TD was located in the TD-resected group.

The pattern of distant metastasis was similar in both groups, except for bone metastasis. The number of patients with bone metastases was significantly higher in the TD-resected group ( $P=0.017$ ) (Table 4).

In c-stage IA patients, there were no significant differences in the primary outcomes between the two groups. More specifically, the 5-year OS rate was 83% in the TD-resected group versus 81% in the TD-preserved group ( $P=0.76$ ; Fig. 1D). The 5-year DFS rate was 92% in the TD-resected group versus 91% in the TD-preserved group ( $P=0.95$ ; Fig. 1E). The 5-year CSS rate was 92% in the TD-resected group versus 96% in the TD-preserved group ( $P=0.64$ ; Fig. 1F).

In c-stage IB–IV patients, there were no significant differences in the primary outcomes between the two groups. More specifically, the 5-year OS rate was 44% in the TD-resected group versus 51% in the TD-preserved group ( $P=0.21$ ; Fig. 1G). The 5-year DFS rate was 46% in the TD-resected group versus 50% in the TD-preserved group

( $P=0.54$ ; Fig. 1H). The 5-year CSS rate was 51% in the TD-resected group versus 58% in the TD-preserved group ( $P=0.30$ ; Fig. 1I).

## Discussion

Our hypothesis was supported by the lack of significant differences between the TD-resected and TD-preserved groups in OS, DFS, and CSS for patients of all stages, c-stage IA, and c-stage IB–IV. In particular, OS and CSS among patients of all stages showed a tendency towards better prognosis in the TD-preserved group than in the TD-resected group, even though the difference was not statistically significant. Similar results can be seen in a previous report; the TD-preserved group had a more favorable recurrence-free survival curve than the TD-resected group among patients who underwent esophagectomy for c-stage II–IV ESCC.<sup>6</sup> Hou et al. also reported that TD ligation during esophagectomy unfavorably impacted OS of patients with esophageal cancer in a multivariate Cox regression analysis.<sup>14</sup>

The TD ascends in the mediastinum close to the esophagus with evidence of tiny direct lymphatic connections between the esophagus and the TD.<sup>15</sup> Thus, TD resection has been recommended for adequate mediastinal lymphadenectomy in order to dissect TDLNs and the adipose tissue surrounding the TD.<sup>5,7</sup> Indeed, there are some detailed reports about the frequency of metastasis to TDLNs.<sup>5,6</sup> However, there are few reports about the positive impact of TD resection on prognosis because the TD is indispensable for immune function and nutrition circulation.<sup>16,17</sup> The TD lets intestinal chyle flow into the venous system in the subclavian region. Chyle contains a combination of lymphatic and intestine-derived substances, including lymphocytes, immunoglobulins, enzymes, and products of digestion.<sup>18</sup> So, continued

interruption of chyle can lead to immunosuppression and impaired B-lymphocyte-mediated immune function.<sup>19-21</sup> Abnormal circulation of immune factors leading to immunosuppression could contribute to worsening OS in the TD-resected group. Thus, the effect of metastatic TDLNs dissection might be weakened by immunosuppression following TD resection. Demonstrating the unnecessary of TD resection, our study could be a milestone for esophageal cancer surgery.

Regarding histologic type, patients with adenocarcinoma were excluded because they made up less than 5% of all patients in this study. We thought that it was better to focus on ESCC rather than a mix of histologic types. However, we speculate that immunosuppression caused by TD resection should also occur in TD-resected patients with adenocarcinoma, just as in ESCC.

Regarding the pattern of initial recurrence, there were no significant differences between the two groups. The fact that the recurrence rate in LNs around the TD in the TD-preserved group was not statistically worse than that in the TD-resected group means that the efficacy of TDLN dissection is low. Conversely, bone clastokine metastasis, a type of distant metastasis, occurred significantly more often in the TD-resected group than in the TD-preserved group. In breast cancer, lysophosphatidylcholines (LPCs) play an important role in regulating bone metastasis.<sup>22</sup> Deficiency of LPCs stimulates tumor cell proliferation, migration, survival, and expression of prometastatic genes. In contrast, administration of lipid osteoclastokines, which includes LPCs, impedes bone metastasis.<sup>22</sup> LPCs, which are phospholipids, constitute the micelle and transit in the TD as chylomicrons. Thus, a higher incidence of bone metastasis in the TD-resected group

might be related to decreased levels of LPCs, even though this theory has only been confirmed in breast cancer.

Regarding short-term outcomes and complications, we obtained some useful knowledge about operative time for the thoracic procedure, number of retrieved mediastinal LNs, rates of chylothorax and left RLN palsy. Longer operative time for the thoracic procedure in the TD-resected group was reasonable. The TD is located within the posterior mediastinum, in the recently defined paraaortic compartment. This compartment is bounded by the aortoesophageal and aortopulmonary ligaments anteriorly and by the spine posteriorly.<sup>23</sup> Thus, resection of the TD from such a complicated area requires more time compared with a TD-preserving procedure. More retrieved mediastinal LNs was seen in the TD-resected group. Resection of TDLNs should contribute to increased number of retrieved LNs in the TD-resected group. The rate of chylothorax was significantly higher in the TD-resected group. Chylothorax is a relatively rare complication, with a reported incidence of 1% to 9%, but is associated with considerable morbidity.<sup>24-27</sup> It is controversial whether TD resection is a risk factor for chylothorax. Some investigators reported that TD resection or prophylactic ligation may be predictors of postoperative chylothorax.<sup>28, 29</sup> Obstructing major lymphatic flow with TD resection might cause leakage in microscopic lymph ducts that had flowed into the TD, leading to chylothorax. The rate of left RLN palsy was significantly higher in the TD-resected group than in the TD-preserved group. As mentioned earlier, the TD is located in the paraaortic compartment.<sup>23</sup> On the other hand, the left RLN is located along the esophagus. The TD and left RLN run parallel in the mediastinum but come close to each other at the thoracic inlet. Thus, during TD resection, injury of the left RLN might occur in this area, leading to RLN

palsy.

This study has some limitations, including its retrospective design and participation from only two centers. Nonetheless, we utilized a database of about 400 cases from two affiliated institutions that used relatively standardized surgical techniques and postoperative management, thus avoiding some of the limitations of multicenter, population-based studies. Moreover, we used strict propensity score matching to minimize selection bias and provide significant insights even though many patients were excluded.

## **Conclusions**

In summary, TD resection does not contribute to improved OS, DFS, or CSS in ESCC in various stages but increases the likelihood of chylothorax and left RLN palsy. Prophylactic TD resection should be avoided in esophagectomy for ESCC.

## **Disclosures**

**Conflicts of interest:** Taro Oshikiri, Gosuke Takiguchi, Susumu Miura, Hironobu Goto, Dai Otsubo, Hiroshi Hasegawa, Masashi Yamamoto, Shingo Kanaji, Kimihiro Yamashita, Takeru Matsuda, Yasuhiro Fujino, Masahiro Tominaga, Tetsu Nakamura, Satoshi Suzuki, and Yoshihiro Kakeji have no conflicts of interest or financial ties to disclose.

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**Figure legends**

Fig. 1

A) The 5-year OS rate for patients of all stages was 60% among the 122 TD-preserved patients versus 49% among the 122 TD-resected patients ( $P=0.08$ ).

B) The 5-year DFS rate for patients of all stages was 57% among the 122 TD-preserved patients versus 53% among the 122 TD-resected patients ( $P=0.35$ ).

C) The 5-year CSS rate for patients of all stages was 70% among the 122 TD-preserved patients versus 58% among the 122 TD-resected patients ( $P=0.08$ ).

OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; TD, thoracic duct.

D) The 5-year OS rate for c-stage IA patients was 81% among the 25 TD-preserved patients versus 83% among the 25 TD-resected patients ( $P=0.76$ ).

E) The 5-year DFS rate for c-stage IA patients was 91% among the 25 TD-preserved patients versus 92% among the 25 TD-resected patients ( $P=0.95$ ).

F) The 5-year CSS rate for c-stage IA patients was 96% among the 25 TD-preserved patients versus 92% among the 25 TD-resected patients ( $P=0.64$ ).

c-stage, clinical stage; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; TD, thoracic duct.

G) The 5-year OS rate for c-stage IB–IV patients was 51% among the 96 TD-preserved patients versus 44% among the 96 TD-resected patients ( $P=0.21$ ).

H) The 5-year DFS rate for c-stage IB–IV patients was 50% among the 96 TD-preserved patients versus 46% among the 96 TD-resected patients ( $P=0.54$ ).

I) The 5-year CSS rate for c-stage IB–IV patients was 58% among the 96 TD-preserved patients versus 51% among the 96 TD-resected patients ( $P=0.30$ ).

c-stage, clinical stage; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; TD, thoracic duct.

Table 1. Demographic and clinical characteristics of all stage patients

|   | Patients of all stages patients                               |  |                     |   |  |                    |
|---|---|--|---------------------|---|--|--------------------|
|   | Entire cohort   |  |                     | Matched cohort  |  |                    |
|   | Patients with<br>thoracic duct resection<br>( <i>n</i> = 132) | Patients with<br>thoracic duct preservation<br>( <i>n</i> = 207) | <i>P</i>            | Patients with<br>thoracic duct resection<br>( <i>n</i> = 122) | Patients with<br>thoracic duct preservation<br>( <i>n</i> = 122) | <i>P</i>           |
| Gender<br>(male/female)                               | 112/20  | 181/26   | 0.497 <sup>a</sup>  | 103/19  | 103/19   | 1.000 <sup>a</sup> |
| Age<br>(years)  | 65 (41–79)  | 66 (27–79)   | 0.138 <sup>b</sup>  | 66  | 65   | 0.445 <sup>b</sup> |
| Tumor location<br>(upper/middle/lower)                | 33/55/44  | 52/83/72   | 0.952 <sup>a</sup>  | 31/50/41  | 28/49/45   | 0.840 <sup>a</sup> |
| Depth of tumor invasion<br>(cT1/2/3)                  | 36/31/65  | 85/45/77   | 0.027 <sup>a</sup>  | 36/27/59  | 37/26/59   | 0.984 <sup>a</sup> |
| Lymph node metastasis<br>(cN negative/positive)       | 54/78   | 92/115   | 0.523 <sup>a</sup>  | 46/76   | 46/76  | 1.000 <sup>a</sup> |
| UICC c-stage<br>(I/II/III/IV)                         | 40/36/50/6  | 74/67/60/6   | 0.264 <sup>a</sup>  | 36/32/48/6  | 37/31/50/4   | 0.925 <sup>a</sup> |
| Preoperative therapy<br>(yes/no)                      | 97/35   | 110/97   | 0.0002 <sup>a</sup> | 87/35   | 87/35  | 1.000 <sup>a</sup> |
| Thoracic procedure<br>(thoracoscopy/open thoracotomy) | 126/6   | 188/19   | 0.112 <sup>a</sup>  | 116/6   | 116/6  | 1.000 <sup>a</sup> |
| Lymph node dissection<br>(two-field/three-field)      | 51/81   | 81/126   | 0.928 <sup>a</sup>  | 49/73   | 46/74  | 0.694 <sup>a</sup> |
| Conduit<br>(stomach/other)                            | 123/9   | 184/23   | 0.187 <sup>a</sup>  | 113/9   | 105/17   | 0.097 <sup>a</sup> |

<sup>a</sup>  $\chi^2$  test, <sup>b</sup> Student's t-test

Table 2. Demographic and clinical characteristics of patients with c-Stage IB–IV disease

|   | Patients of c-Stage IB–IV                                     |  |                    |  |   |                    |
|---|---|--|--------------------|--|---|--------------------|
|   | Whole cohort  |  |                    | Matched cohort   |   |                    |
|   | Patients with<br>thoracic duct resection<br>( <i>n</i> = 107) | Patients with<br>thoracic duct preservation<br>( <i>n</i> = 146) | <i>P</i>           | Patients with<br>thoracic duct resection<br>( <i>n</i> = 96) | Patients with<br>thoracic duct preservation<br>( <i>n</i> = 96) | <i>P</i>           |
| Gender<br>(male/female)                               | 92/15   | 124/22   | 0.815 <sup>a</sup> | 81/15  | 79/17   | 0.699 <sup>a</sup> |
| Age<br>(years)  | 65  | 66   | 0.208 <sup>b</sup> | 64   | 65  | 0.438 <sup>b</sup> |
| Tumor location<br>(upper/middle/lower)                | 24/45/38  | 37/53/56   | 0.644 <sup>a</sup> | 19/43/34   | 27/34/35  | 0.293 <sup>a</sup> |
| Depth of tumor invasion<br>(cT1/2/3)                  | 11/31/65  | 24/45/77   | 0.291 <sup>a</sup> | 11/26/59   | 11/26/59  | 1.000 <sup>a</sup> |
| Lymph node metastasis<br>(cN negative/positive)       | 29/78   | 31/115   | 0.278 <sup>a</sup> | 20/76  | 20/76   | 1.000 <sup>a</sup> |
| UICC c-stage<br>(IB/II/III/IV)                        | 15/36/50/6  | 13/67/60/6   | 0.214 <sup>a</sup> | 11/31/49/5   | 11/32/48/5  | 0.999 <sup>a</sup> |
| Preoperative therapy<br>(yes/no)                      | 96/11   | 108/38   | 0.002 <sup>a</sup> | 85/11  | 85/11   | 1.000 <sup>a</sup> |
| Thoracic procedure<br>(thoracoscopy/open thoracotomy) | 102/5   | 129/17   | 0.052 <sup>a</sup> | 91/5   | 91/5  | 1.000 <sup>a</sup> |
| Lymph node dissection<br>(two-field/three-field)      | 42/65   | 52/94  | 0.554 <sup>a</sup> | 38/58  | 32/64   | 0.368 <sup>a</sup> |
| Conduit<br>(stomach/other)                            | 99/8  | 126/20   | 0.119 <sup>a</sup> | 88/8   | 81/15   | 0.120 <sup>a</sup> |

<sup>a</sup>  $\chi^2$  test, <sup>b</sup> Student's t-test, c-stage; clinical stage, UICC; Union for International Cancer Control.

Table 3. Operative outcomes in patients with thoracic duct resection or preservation

|   | Patients with<br>thoracic duct resection<br>( <i>n</i> = 122) | Patients with<br>thoracic duct preservation<br>( <i>n</i> = 122) | <i>P</i>           |
|---|---|--|--------------------|
| Operative time for the thoracic procedure (min)                             | 313 ± 59  | 289 ± 80   | 0.009 <sup>c</sup> |
| Number of retrieved mediastinal nodes                                       | 25 ± 10   | 22 ± 11  | 0.005 <sup>c</sup> |
| Chylothorax (grade <sup>a</sup> ≥ II) (yes/no)                              | 3/119   | 0/122  | 0.041 <sup>d</sup> |
| Pneumonia (grade <sup>a</sup> ≥ II) (yes/no)                                | 28/94   | 19/103   | 0.144 <sup>d</sup> |
| Leakage (grade <sup>a</sup> ≥ II) (yes/no)                                  | 22/100  | 19/103   | 0.608 <sup>d</sup> |
| Left recurrent laryngeal nerve palsy<br>(grade <sup>a</sup> ≥ II) (yes/no)  | 28/94   | 14/108   | 0.018 <sup>d</sup> |
| Right recurrent laryngeal nerve palsy<br>(grade <sup>a</sup> ≥ II) (yes/no) | 12/110  | 5/117  | 0.078 <sup>d</sup> |
| Postoperative hospital stay (days) <sup>b</sup>                             | 33  | 27   | 0.045 <sup>e</sup> |

<sup>a</sup> Postoperative morbidity was analyzed according to the Clavien-Dindo classification,

<sup>b</sup> Data are expressed as medians, <sup>c</sup> Student's *t*-test, <sup>d</sup>  $\chi^2$  test, <sup>e</sup> Mann-Whitney *U* test

Table 4. Initial recurrence patterns in patients with thoracic duct resection or preservation

| Recurrence location                 | Patients with<br>thoracic duct resection<br>(n = 122) | Patients with<br>thoracic duct preservation<br>(n = 122) | <i>P</i>           |
|-------------------------------------|---|--|--------------------|
| Mediastinum                         | 23 (18.9%)  | 18 (14.8%)   | 0.392 <sup>a</sup> |
| Area around the TD                  | 1 (0.8%)  | 2 (1.6%)   | 0.561 <sup>a</sup> |
| Local (area near the primary tumor) | 6 (4.9%)  | 3 (2.5%)   | 0.308 <sup>a</sup> |
| Distant                             | 30 (24.6%)  | 21 (17.2%)   | 0.137 <sup>a</sup> |
| Pleural dissemination               | 6 (4.9%)  | 5 (4.1%)   | 0.758 <sup>a</sup> |
| Lung                                | 12 (9.8%)   | 11 (9.0%)  | 0.827 <sup>a</sup> |
| Liver                               | 8 (6.6%)  | 8 (6.6%)   | 1.000 <sup>a</sup> |
| Bone                                | 8 (6.6%)  | 1 (0.8%)   | 0.017 <sup>a</sup> |
| Brain                               | 1 (0.8%)  | 1 (0.8%)   | 1.000 <sup>a</sup> |
| Other                               | 6 (4.9%)  | 3 (2.5%)   | 0.308 <sup>a</sup> |

<sup>a</sup>  $\chi^2$  test, TD;thoracic duct

