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# Trends in Lymphadenectomy for Esophageal/Esophagogastric Junction Cancer

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**Abstract:** Lymph node (LN) metastasis is recognized to be an important prognostic factor for esophageal cancer (EC). However, there is no worldwide uniform classification system, and no consensus exists on the extent of the lymphadenectomy. Recently, an international observational cohort study was conducted to evaluate the distribution of LN metastasis in EC patients. Moreover, this could be a milestone to establish a standard classification system and provide new insights to determine the extent of LNs that should be target for treatment. With regard to surgical procedures, three-field lymphadenectomy seems to be promising to improve the prognosis with EC patients. However, extended lymphadenectomy could lead to postoperative complications. The development of minimally invasive esophagectomy (MIE) has allowed us to retrieve cervical paraesophageal nodes without cervical incision and reduce the incidence of postoperative complications. Therefore, it may be possible that the era of MIE could propose the modern extent of LN dissection in the future. Additionally, one of the key components in lymphadenectomy for EC was thoracic duct and surrounding tissues. Although there is some evidence of LN metastasis surrounding the TD, the survival benefit of TD resection is still debatable. With regard to esophagogastiric junction cancer, the extent of LN dissection could be determined by the length of esophageal involvement. We believe further understanding of LN metastasis of EC patients will contribute to establish a global standard of treatment and improve their prognosis.

**Keywords:** esophageal cancer; lymph node metastasis; three field lymph node dissection; minimally invasive esophagectomy

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## 1. Introduction

Lymph node (LN) metastasis is recognized to be an important prognostic factor for esophageal cancer (EC) [1]. Even in those with pT1b tumors, the incidence of lymph node metastasis reaches 45% [2]. Because the esophagus connects the hypopharynx and the stomach, it crosses three different compartments in the human body (the neck, mediastinum, and the upper abdomen). In all three compartments, the esophagus has vascular and lymphatic connections [3]. Additionally, it is also reported that LN metastasis skips to different compartments of regional lymph nodes in 50 to 60% of EC [2]. However, not only is the classification of LN stations not universal, but the extent of lymphadenectomy also varies worldwide. Although esophagectomy is the mainstream of treatment, multidisciplinary treatment strategies including surgery, chemotherapy, and radiation therapy have been required to improve the outcome of survival of EC [4]. The JCOG 9907 trial is a multicenter phase III trial that compared the survival benefit between preoperative chemotherapy using 5-fuorouracil + cisplatin (CF) followed by esophagectomy and esophagectomy followed by postoperative CF therapy [5]. Neoadjuvant chemotherapy was superior to postoperative chemotherapy, and this trial became the milestone in Japan that declared that standard treatment for locally advanced EC should be neoadjuvant chemotherapy (CF regimen) followed by esophagectomy. To achieve better survival, JCOG ran a three-arm phase III

trial (JCOG 1109) to assess the superiority of CF plus docetaxel (DCF) over CF and the superiority of chemoradiotherapy with CF over CF as preoperative therapy [6]. The result of the primary endpoint was recently reported and revealed that DCF significantly improved the survival of CF, whereas chemoradiotherapy with CF did not [7]. We conducted a nationwide retrospective study using real-world data from 85 esophageal centers in Japan [8]. The results showed that DCF had better survival advantage of both OS and RFS than CF for patients with ESCC who were 75 years old or younger, while it might not be feasible for elderly patients [9]. This result suggests that DCF should be a standard regimen for preoperative chemotherapy for locally advanced ESCC. On the contrary, in Western countries, neoadjuvant chemoradiotherapy (CRT) is the golden standard for locally advanced resectable EC, based on the result of a CROSS trial that demonstrated the superiority of neoadjuvant CRT consisting of 41.4 Gy irradiation combined with carboplatin plus paclitaxel followed by surgery [10]. Moreover, the presence of the immune checkpoint inhibitor has created higher expectations for better survival. CheckMate-577 trial is a global, randomized, phase III trial to evaluate the survival benefit of the checkpoint inhibitor, nivolumab, as adjuvant therapy for patients who had received neoadjuvant CRT and undergone complete resection. This demonstrated that adjuvant nivolumab therapy provided better DFS than the placebo group. Thus far, many clinical trials have sought the possibility to achieve the better prognosis of EC. However, we believe it is essential for further understanding of LN metastasis of EC, and establish the optimal extent of LN dissection. In this review, we will discuss the LN metastasis pattern of EC and the extent of sufficient lymphadenectomy. Additionally, we will discuss the new trend of LN dissection as the era of minimally invasive esophagectomy has arisen.

## 2. The Distribution of Metastatic LNs for Esophageal Cancer

### *2.1. Systems for Classifying Lymph Node Metastasis in Esophageal Cancer*

Although it is important to discover and predict the pattern of LN metastasis, there is still no worldwide uniform classification system. There are two different systems for classifying lymph node metastasis in esophageal cancer: one is the 12th edition of the "Japanese Classification of Esophageal Cancer" published by the Japanese Esophageal society (JES); the other is the "Cancer Staging Manual" by American Joint Committee on Cancer (AJCC) [11–13].

The largest difference between the two classifications is the definition of cervical lymph nodes. By the AJCC system, cervical lymph nodes, except for station 1 and level VI and VII (head and neck AJCC cancer staging), are not considered as locoregional lymph node metastases but as extraregional lymph node as M-disease, regardless of the location of the tumor. The latest JES system has attempted to unify with the AJCC classification and has defined supraclavicular lymph nodes as M1a lymph node when the tumor is located at the thoracic part. In clinical practice in Japan, treatment strategy would be determined by the classification of JES.

Although both classifications can be used to name each station, the heterogeneity makes it challenging to compare studies of LN metastasis of EC. Hagens et al. proposed a systematic review to distribute the patterns of LN metastasis in patients with esophageal adenocarcinoma or squamous cell carcinoma [14]. They reported that both esophageal adenocarcinoma and squamous cell carcinoma can metastasize to cervical, thoracic, and abdominal lymph node stations, regardless of the location of the primary tumor.

Recently, the TIGER study was conducted to evaluate the distribution of lymph node metastases in EC specimens following transthoracic esophagectomy with two- or three-field lymphadenectomy [15]. They combined the classification of JES 11th edition and the AJCC 8th edition as the TIGER classification. This study may contribute to the global use of one classification system for all EC patients, and support guidelines on defining the extent of lymphadenectomy with regard to different tumor characteristics.

### *2.2. Applying the Concept of Sentinel Lymph Node for Esophageal Cancer*

Because EC is known to have a multidirectional lymphatic flow from the primary lesion even in those with early stage, Takeuchi et al. previously attempted to identify the sentinel lymph node (SLN) for patients with T1N0 or T2N0 EC [16]. The SLN is defined as the LN that is/are first to receive lymphatic drainage from the tumor site [17]. In this study, SLNs were detected by a radio-guided method which was used previously for mapping SLNs in gastrointestinal surgeries [18]. Seventy-five patients who underwent standard radical esophagectomy were enrolled. SLNs were successfully identified in 71 (95%) patients, and the accuracy was 94% (67/71). Distribution of identified SLNs was widely spread from cervical to abdominal areas. In upper thoracic esophageal cancer, the lymph nodes along the bilateral recurrent laryngeal nerve chain were identified most frequently. However, 25% of those showed SLNs along the left gastric artery. With regard to lower thoracic EC, SLNs were mainly detected in the abdominal area but 20% of cases identified SLNs in the right recurrent nerve. This may indicate that the lymphatic flow of EC is abundant and LN metastasis can be found to other regional LN stations. As such, the extended esophagectomy with three-field lymphadenectomy may be a reasonable procedure for the wide SLN distribution and unpredictable metastatic patterns. Although insufficient lymphadenectomy may have risk for understaging and undertreating patients, an extensive lymphadenectomy may result in more postoperative complications, which makes it controversial as to whether three-field lymphadenectomy should be performed [19]. SLN mapping may provide significant information to perform individualized selective lymphadenectomy. On the contrary, Gabrielson et al. detected SLNs with advanced EC patients and reported that the sensitivity was low to detect SLNs [20]. This underlies the difficulty of recognizing the distribution of LN metastasis to standardize the extent of the radiation field and lymphadenectomy in EC.

### *2.3. Distribution of LN Metastasis in EC Patients*

Hagens et al. reported a systematic review to identify the distribution pattern of LN metastasis in relation to histology, tumor location, and T-stage in patients with EC [14]. A total of 8952 patients were included. Interestingly, both squamous cell carcinoma and adenocarcinoma metastasize to cervical, thoracic, and abdominal lymph node stations, regardless of the location of the primary tumor. With regard to patients with squamous cell carcinoma, those with upper thoracic tumor LN metastases were most frequently seen along the right recurrent nerve (60%) followed by cervical paraoesophageal lymph nodes (right: 34% and left: 22%). For those with middle thoracic tumor, the prevalence was highest along the right recurrent nerve (23%), right cervical paraoesophageal lymph nodes (24%), and middle thoracic paraoesophageal lymph nodes (23%). Patients with a tumor in the lower thoracic esophagus had the highest lymph node metastases along the left gastric artery (28%) and the lower thoracic esophagus (23%).

For adenocarcinoma, 8% of tumors were located in the distal esophagus and 92% were located at the esophagogastric junction (EGJ). Patients with tumors located in the distal esophagus revealed lymph node metastasis in the lower mediastinal region and the abdominal regions: 71% each. Surprisingly, 35% patients had lymph node metastasis in the cervical region.

### *2.4. Distribution of LN Metastasis in EGJ Patients*

EGJ adenocarcinoma is divided into three types by the Siewert classification based on the epicenter of the tumor [21]. Although subtotal esophagectomy with proximal gastrectomy was standard for Siewert type I (located 1 to 5 cm above the EGJ), the optimal surgical procedure for Siewert type II (located 1 cm above to 2 cm below the EGJ) was not standardized. This made it difficult to investigate the distribution of LN metastasis of EGJ as the lymphadenectomy field differed in each case. Kurokawa et al. conducted a prospective nationwide study to identify the metastasis rate of each mediastinal and abdominal LN to determine the optimal extent of LN dissection for both squamous cell

carcinoma and adenocarcinoma [22]. Patients with cT2-T4 tumor located within 2 cm of the EGJ were enrolled. A total of 371 patients were included, and 358 patients underwent surgical resection. More than 10% LNs were found with metastasis in the perigastric station. The metastasis rate in the mediastinal nodes was related to the length of involvement of esophagus. The metastasis rate of lower thoracic paraesophageal LNs was consistently greater than 10% when the esophageal involvement exceeded 2 cm. However, the metastasis rate of supradiaphragmatic nodes and the posterior mediastinal nodes were consistently less than 5% unless the esophageal involvement exceeded 4 cm. This is supported by the results of a Japanese randomized controlled trial (JCOG 9502) that compared the dissection of lower mediastinal nodes in patients with mainly Siewert type II and III adenocarcinoma with esophageal involvement less than 3 cm [23,24]. In contrast, upper mediastinal region LNs were found with metastasis more than 10% when the esophageal involvement exceeded 4 cm.

### *2.5. LNs around the Thoracic Duct*

The thoracic duct (TD) receives the lymphatic fluid from the entire body, except for the right hemithorax, right head and neck, and the right arm. It commonly terminates at or near the left venous angle [25]. The TD is the largest lymphatic vessel in the human body that transports up to 3 L or more of lymph back to the systemic circulation each day [26]. To discuss the clinical meaning of TD resection, it is important to consider the lymphatic drainage of cancer cells to the LNs surrounding the TD (TDLN). Udagawa et al. described TDLNs as part of the posterior mediastinal nodes [27]. However, because the LNs and the adipose tissue surrounding the TD are wrapped with connective tissue and membrane, they are easily differentiated from periesophageal and other posterior mediastinal nodes [27]. Ohkura et al. described a retrospective study to investigate the efficacy and prognostic impact of TDLNs dissection. A total of 1211 patients were included and 607 retrieved TDLN resection. The metastatic rates in all patients were 7.3%, while those in pT0–2 were 2.2% and those in T3–4 were 11.5%. By tumor site, the metastatic rate in TDLNs with patients pT0–2 was Ut/Mt/Lt = 1.1%/2.4%/2.4%, and in pT3–4 patients it was Ut/Mt/Lt = 7.7%/14.5%/8.4%. These rates show that those with advanced tumor located in the Mt have highest possibility of metastases in TDLNs. Previously, we also analyzed the distribution of TDLN metastasis. Two hundred and thirty-two patients were enrolled and their clinical record were investigated retrospectively [28]. Interestingly, the rate of TDLNs was similar to that of Ohkura's study. In total, 7.0% (17/232) of patients were observed with metastasis. In terms of the depth of the primary tumor, 2.0% were found with pT1–2 and 17% were found with pT3–4. Analyzing the influence of location of the primary tumor, TDLN metastasis were observed with cases of Ut/Mt/Lt = 29%/71%/12%, which indicates that TDLN metastasis occurred frequently at the mid-thoracic esophagus. Recently, Defize et al. reported the metastasis rate of TDLNs. Unlike the previous studies, they analyzed patients from Europe which indicate that the histology is different from other studies [29]. Patients who underwent esophagectomy with a two- or three-field lymphadenectomy and resection of the TD compartment were included. A total of 117 patients were included; among them, 73% of them were proven to have adenocarcinoma histologically. Nine patients (7.7%) had metastasis of TDLN, and all of the patients were diagnosed with pathologic T3 stage. Surprisingly, in one patient, the metastatic TDLNs were the only tumor-positive LNs in the resection specimen. Because the metastasis rate did not differ with the three studies, this may indicate that LN metastasis is a phenomenon that occurs in addition to the histology of the tumor.

## 3. Surgical Approaches to Eliminate Wide Range of LN Metastases

### *3.1. Three-Field LN Dissection in Esophagectomy*

Because of the high incidence rate of lymph node metastasis, one of the standard surgical procedure to regulate the extent of LN metastasis that has been developed is three-field LN dissection (3FD) [30]. The definition of 3FD is as follows: nodal tissue compassing

upper abdominal, inferior, middle, and superior mediastinal lymph nodes, and inferior cervical nodes [31]. On the contrary, two-field LN dissection (2FD) is the same as 3FD except for removal of the cervical nodes [31]. There are several reports that claim better survival benefits of 3FD than 2FD [32–34]. However, there are concerns that 3FD has a higher risk for surgical complications. Wang et al. conducted a meta-analysis to compare the short- and long-term outcomes between 3FD and 2FD [35]. A total of 1676 patients with squamous cell carcinomas were included. Because there was no significant difference between the two lymphadenectomies of OS (95% CI: 0.90–1.21, $p = 0.56$), and 3FD caused higher levels of intraoperative blood loss and the morbidity of anastomotic fistula, they concluded that 2FD should be recommended for EC patients with squamous cell carcinomas. On the contrary, Li et al. conducted a randomized phase III trial to compare the OS, morbidity, and mortality between 3FD and 2FD with patients with EC patients with squamous cell carcinomas who received neither neoadjuvant chemotherapy nor radiotherapy [36]. A total of 400 patients were assigned randomly to 2FD or 3FD, including 200 patients in each group. Although the results of survival are still awaited, the severity of postoperative complications was comparable between the two groups. With regard to recent publications, Bona et al. conducted a systematic review to compare the long-term survival between 3FD and 2FD [37]. A total of 3431 patients were included (3FD: 1664 patients vs. 2FD: 1767 patients). Five-year OS was significantly higher with those who received 3FD (95% CI: 0.71–0.90, $p < 0.001$), and no significant differences were found in terms of postoperative mortality, anastomotic leakage, pulmonary complications, chylothorax, and recurrent nerve palsy.

### *3.2. LN Dissection around the Thoracic Duct*

Although direct lymphatic drainage to the thoracic duct (TD) from the submucosa is common, especially for the left esophageal wall [3], the significance of TD resection is still controversial. Previously, we showed that minimally invasive transthoracic esophagectomy (TTE) with extensive LN dissection along with TD resection improved survival in cStage I esophageal cancer [38]. Moreover, we analyzed the survival of those who had metastasis in LNs surrounding the TD (TDLN), and TDLN metastasis was revealed to be an independent prognostic factor for both RFS and OS [28]. Ohkura et al. also showed that TDLN resection was at least as effective as that of other group-2 or-3 LNs, including thoracic paraaortic LNs [39]. On the contrary, a recent study claimed that although TD resection was accompanied by a relatively high number of retrieved mediastinal LNs and relatively less LN recurrence, it did not improve the survival of patients with esophageal cancer [40]. Overall, the survival benefit of resection of the TD and its surrounding adipose tissue remains uncertain and a prospective randomized trial is necessary to conclude this debate.

With regard to the survival benefit of TDLNs dissection, little is known of the physiological effect of TD resection. After a fatty meal, dietary lipids enter the venous system in the small intestine through the TD [41]. As such, TD resection may have a negative impact on absorption of fat. Fujisawa et al. compared the change of body composition before and one year after esophagectomy, with or without TD resection [42]. Fifty-one cases were classified as TD-preserved group, while 123 cases were included as TD-resected group. In both groups, body fat mass continuously decreased over 1 year after surgery. Skeletal muscle mass decreased 1 month after surgery but maintained in the same state until 1 year after surgery. The decrease of body fat mass was statistically greater 1 year after surgery with patients who underwent TD resection (TD preserved—33.14% vs. TD resected—41.9%, $p = 0.021$). However, the change of skeletal muscle mass did not differ after TD resection (TD preserved—4.19% vs. TD resected—3.76%, $p = 0.858$). They speculated that because TD plays an important role in transporting digestive fat, TD resection may have interfered with this function. On the contrary, muscle mass could be influenced by many factors such as perioperative rehabilitation and nutrition counseling, and TD resection may not be a strong factor to deteriorate skeletal muscle mass. We previously analyzed the long-term impact of TD resection on body composition by analyzing patients who had no recurrence in the

first three years after esophagectomy for esophageal cancer. Body composition of those who met their five-year follow-up without recurrence was also analyzed. We recruited patients with no recurrence to exclude confounding effect of deteriorated nutrition status by cancer cachexia. Interestingly, the trend of decrease in body composition in their study was similar with the trend in our study [43]. TD resection was a risk factor for loss of body fat in the first three years after esophagectomy. However, this improved within five years after esophagectomy. Moreover, the change of muscle mass was not affected after TD resection. Although there are few reports that claim body fat is essential for quality of life, muscle wasting after surgery has been multiply reported to be associated with poor quality of life [44,45]. Because body fat catches up in the long term, and body fat mass was not influenced by TD resection, we concluded that TD resection was acceptable on nutrition status. We summarize previous statements of TD resection in Table 1.

**Table 1.** Previous statements of resection of TD.

| Author | Patient Inclusion Period | N | Statement |
|---|---|---|---|
| Matuda [28] | 2013–April 2018 | 232 | TDLN metastasis is a strong prognostic indicator in ESCC. |
| Ohkura [39] | 1984–December 2020 | 1211 | TDLNs dissection is evident in cases with invasion depth or greater than T3. |
| Defize [29] | July 2017–May 2020 | 117 | TDLN metastasis is proven in both ESCC and adenocarcinoma of the esophagus. |
| Oshikiri [40] | 2007–2012 | 12,237 | TD resection did not improve prognosis in patients with EC. |
| Fujisawa [42] | October 2015–March 2019 | 174 | TD resection decreased body fat in the short term after esophagectomy with no influence on muscle mass. |
| Nishimura [43] | January 2006–December 2018 | 217 | Decrease in body fat by TD resection will recover in the long term after surgery. Muscle mass will not be affected by TD resection. |

TD, thoracic duct; TDLNs, lymph nodes surrounding the thoracic duct; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer.

### *3.3. Can We Omit Prophylactic Supraclavicular LN Dissection in the New Era of Modern Lymphadenectomy for EC Patients?*

Minimally invasive esophagectomy (MIE) is being increasingly implemented because they have significantly reduced the incidence of postoperative complications, especially respiratory complications, compared to open esophagectomy [46,47]. Randomized control trials have shown that MIE reduced pulmonary and cardiac postoperative morbidity; however, the survival benefit of MIE has not been proven [48,49]. MIE is expected to be beneficial for survival because they are reported to be able to retrieve more LNs than open procedures [50]. Kalf et al. conducted a nationwide propensity score matched cohort to compare the long-term survival following MIE versus open esophagectomy (OE) for EC patients [51]. A propensity matched analysis for MIE versus OE was performed separately for transthoracic and transhiatal esophagectomy. A total of 1036 patients were included in this study and the 5-year OS was comparable between MIE and OE (transthoracic MIE 49.2% vs. OE 51.1%, $p = 0.695$; transhiatal MIE 48.4% vs. OE 50.7, $p = 0.832$). Moreover, MIE retrieved more LNs in both procedures. Currently, a randomized phase III trial to confirm the noninferiority of MIE to OE in terms of overall survival is running [52]. While only patients with histology of squamous cell carcinoma were included, this was the first prospective randomized trial to analyze the long-term efficacy of MIE.

In the OE approach, resection of recurrent laryngeal nerve (RLN) and the cervical paraesophageal nodes through a paratracheal approach is difficult because the surgical space of the cervicothoracic junction is narrow from this view [53]. Therefore, bilateral neck incisions are usually needed. On the contrary, MIE can provide a better illumination and exposure of this narrow space, and it is convenient to perform en bloc dissection of LNs along the RLN and the cervical paraesophageal nodes. Additionally, there is no clear

evidence that supports or rejects prophylactic supraclavicular LNs (SCLNs) dissection [54]. Postoperative SCLN metastasis can often be managed by either surgery or chemoradiation at the time of relapse. Moreover, in previous studies, SCLN dissection could increase the incidence of postoperative complication such as recurrent laryngeal nerve palsy [55]. A multicenter randomized trial to confirm the noninferiority of esophagectomy with D2 lymphadenectomy except for SCLN to standard D2 lymphadenectomy in terms of overall survival (JCOG 2013) has been running. For these reasons, it may be possible for surgeons to omit the right cervical incision [56]. The era of MIE could lead to a modern extent of LN dissection [57].

## 4. Future Directions

Controlling LN metastasis is the key to improve EC patients' survival. For further understandings, a global standard to categorize LN stations is expected. Sufficient lymphadenectomy is one of the gold standard treatments to conquer EC. However, the development of MIE has allowed us to retrieve more LNs in a better illumination. For this progress, a new concept of extent of lymphadenectomy may arise in the future.

## 5. Conclusions

EC is an aggressive disease that can metastasize to cervical and thoracic, as well as abdominal LN stations, regardless of the location of the primary tumor. Despite the increasing incidence of EC, there is no worldwide uniform classification system, and no consensus exists on the extent of the radiation field and lymphadenectomy. Sufficient lymphadenectomy involving three-field dissection seems to be a promising strategy to receive more LNs and improve the prognosis. However, the development of MIE has allowed us to retrieve cervical paraesophageal nodes during the thoracic approach without cervical incision. Therefore, it may be possible that the era of MIE could lead to a modern extent of LN dissection.

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## Abbreviations

| | |
|---|---|
| LN | lymph node |
| JES | Japanese Esophageal society |
| AJCC | American Joint Committee on Cancer |
| CRT | chemoradiotherapy |
| SLN | sentinel lymph node |
| EGJ | esophagogastric junction |
| Three-FD | three field lymph node dissection |
| Two-FD | two field lymph node dissection |
| TTE | trans-thoracic esophagectomy |
| TD | thoracic duct |
| TDLN | lymph nodes surrounding the thoracic duct |
| MIE | minimally invasive esophagectomy |
| OE | open esophagectomy |
| RLN | recurrent laryngeal nerve |
| SCLN | supraclavicular lymph node |

| | |
|---|---|
| ESCC | esophageal squamous cell carcinoma |
| EC | esophageal cancer |
| JCOG | Japan Clinical Oncology Group |

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