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ORIGINAL RESEARCH

Minimally Invasive Esophagectomy with Thoracic Duct Resection Post Neoadjuvant Chemoradiotherapy for Carcinoma Esophagus—Impact on Lymph Node Yield and Hemodynamic Parameters

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Abstract

Background Neoadjuvant therapy followed by surgery is the current recommended treatment for locally advanced esophageal carcinoma. Thoracic duct (TD) resection was indicated for radical mediastinal lymphadenectomy. However, TD resection can cause hemodynamic disturbances. The presence of metastasis in TD has not been previously studied.

Methods Twenty-two patients who underwent minimally invasive esophagectomy with D2 lymphadenectomy after neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma were analyzed. Ten patients had their TD resected from thoracic inlet till the esophageal hiatus. Multiple histopathological sections of the TD were examined for evidence of tumor spread. Intraoperative and immediate (48 h) postoperative hemodynamic parameters, lymph node yield, and postoperative morbidity were compared between TD-resected and TD-preserved groups.

Results The median postoperative day 1 fluid requirement (3310 mL vs. 2875 mL, $P = 0.059$) and the median postoperative day 2 pulse rate were higher in the TD-resected group (111/min vs. 95/min, $P = 0.043$). There was no significant difference in the intraoperative fluid infusion, blood loss, urine output, mean blood pressure, pulse rate, postoperative urine output, and mean blood pressure between two groups. Median (range) mediastinal lymph node count was similar in TD-resected and TD-preserved groups [15(11–32) vs. 14(9–31), $P = 0.283$]. Pathological examination of TD did not reveal tumor cells in any of the patients. There was no significant difference in the postoperative morbidity between two groups except for cervical anastomotic dehiscence ($P = 0.007$).

Conclusions Minimally invasive esophagectomy with TD resection causes minor hemodynamic changes in the immediate postoperative period, without adversely affecting the postoperative outcome. In the setting of neoadjuvant chemoradiotherapy, TD resection does not increase lymph node yield.

Keywords Thoracic duct · Esophagectomy · Esophageal cancer · Thoracoscopy · Laparoscopy

Introduction

Esophageal carcinoma is an aggressive tumor with a propensity for early lymph node metastasis. Studies have shown that the number of dissected lymph nodes is an important prognostic factor [1, 2]. Hence, transthoracic esophagectomy with radical lymphadenectomy has been recognized as one of the standard treatment for esophageal cancer [3, 4]. Despite radical lymphadenectomy, 5-year survival rate rarely exceeds 40% with surgery alone. Hence, National Comprehensive Cancer Network (NCCN) guidelines advocate chemoradiotherapy followed by surgical resection as the standard treatment option for patients with non-cervical stages IB, II, III, and IVA esophageal cancer [5]. In the era of neoadjuvant therapy with a focus on the quality of life following esophagectomy, the role of radical lymphadenectomy has been questioned [6]. However, studies have shown that the therapeutic value of lymph node dissection at different lymph node stations expressed as efficacy index was not altered by

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neoadjuvant therapy [7]. The advent of minimally invasive approaches to esophagectomy facilitates performance of radical lymphadenectomy without adversely affecting the postoperative outcome [8].

Thoracic duct (TD) ascends in the mediastinum in close relation to the esophagus with evidence of tiny direct lymphatics from the esophagus into TD [9, 10]. Hence, resection of TD along with TD lymph nodes was indicated for adequate mediastinal lymphadenectomy [12]. However, TD resection was reported to cause intravenous volume loss, hemodynamic disturbances and delay in ensuing enteral feeds following surgery [12, 13]. In animal models, resection of TD has been shown to cause liver damage by an increase in the amount of endotoxins exposure to hepatocytes [14]. The presence of metastasis in TD per se has not been previously studied. Hence, this study was conducted to assess the hemodynamic changes following TD resection and to determine whether TD resection influences lymph node yield in patients receiving neoadjuvant treatment for esophageal carcinoma.

Materials and Methods

This study was a retrospective analysis of patients who underwent minimally invasive esophagectomy post neoadjuvant chemoradiotherapy for locally advanced squamous cell carcinoma of the esophagus between May 2014 and August 2016. Patients who underwent upfront surgery and those who underwent non-curative resection were excluded from the analysis. After a diagnostic upper gastrointestinal endoscopy and biopsy, preoperative staging were done with contrast enhanced computed tomography neck, thorax, and abdomen. Endoscopic ultrasound and positron emission tomography were not routinely performed for staging. Neoadjuvant chemoradiotherapy was given to patients with T2 and above primary tumor or node positive tumor as per CROSS protocol that includes five cycles of weekly administration of carboplatin and paclitaxel and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) [15].

Minimally invasive esophagectomy was performed using the thoracoscopic approach in a prone position with single lumen endotracheal tube intubation and double lung ventilation. A D2 radical lymphadenectomy as advocated by the 10th edition of Japanese classification of esophageal cancer was performed [16]. In brief, a D2 lymphadenectomy requires clearance of group 1 and group 2 lymph nodes. Lymph node stations classified as groups 1 and 2 vary according to the location of the tumor. For lower thoracic tumor, a D2 lymphadenectomy requires clearance of lymph node stations 106 rec (right and left recurrent laryngeal nerve nodes, 107 (subcarinal nodes), 108 (middle thoracic paraesophageal nodes), 109 (main bronchus nodes), 110 (lower thoracic paraesophageal nodes), 112aoA (anterior thoracic paraaortic nodes), and 112pul (pulmonary ligament nodes) in the mediastinum. Also, lymph node stations 1 (right paracardial nodes), 2 (left paracardial nodes), 3a (lesser curvature lymph nodes along the branches of the left gastric artery), 7 (left gastric artery nodes), 9 (celiac artery nodes), and 20 (esophageal hiatus nodes) are cleared in the abdomen and station 101 (cervical paraesophageal nodes) is cleared in the neck for a lower thoracic tumor. Abdominal lymphadenectomy and gastric mobilization were done using laparoscopic approach. Gastric conduit formation was done through a mini-laparotomy. Stomach was used as a conduit in all patients and was pulled up through posterior mediastinum for cervical anastomosis. All patients underwent single-stapled cervical esophago gastric anastomosis by modified Collard's technique [17]. Ten patients had their TD resected as a part of their lymph node dissection. TD was resected from the level of thoracic inlet till the lower esophageal hiatus in the diaphragm and the ends of TD were secured with endoclips. Accordingly, patients were divided into TD-resected and TD-preserved groups.

The data collected included patient demographics, the tumor histologic type and location, the depth of tumor invasion, and the lymph node yield. Intraoperative, immediate (48 h) postoperative hemodynamic parameters and fluid requirements were also noted. Operative mortality was defined as death within 30 days after surgery or before discharge from the hospital whichever is later. Morbidity specific to esophagectomy was classified as per the recommendations of esophagectomy complication consensus group [18]. The pathologic response in the present study was assessed according to Becker criteria [19]. Becker's grade 1A is no residual tumor cells suggestive of pathological complete response (PCR), grade 1B is $< 10\%$ residual cells, grade 2 is 10–50% residual tumor cells, whereas $> 50\%$ tumor cells or no signs of neoplastic regression is grade 3. Multiple histopathological sections of TD were examined for the presence of tumor spread. Hemodynamic parameters and lymph node yield were compared between TD-resected and TD-preserved groups. The extent of tumor spread was recorded according to the seventh edition of TNM classification (American Joint Committee on Cancer Staging, AJCC staging) [20].

Statistical significance of parametric variables was assessed by Independent Student's t test and non-parametric variables by Mann-Whitney U test. A P value of less than 0.05 was considered statistically significant. The statistical tests were done using SPSS 19 software.

Results

During the study period, 26 patients diagnosed to have squamous cell carcinoma of the thoracic esophagus with or without the involvement of esophago gastric junction were operated. Two patients, who underwent non-curative resection due to tracheal involvement, were excluded. Another two patients, who underwent upfront surgery in view of poor compliance for neoadjuvant therapy, were also excluded from the study. Twenty-two patients, included in the study, received neoadjuvant chemoradiotherapy as per CROSS protocol. The demographic and clinicopathological parameters of patients included in the study are summarized in Table 1. Majority of the patients belonged to their fifth and sixth decade with almost equal sex distribution. All patients had locally advanced squamous cell carcinoma of middle or lower thoracic esophagus with esophago gastric junction involvement in three patients.

Esophagectomy was done by the minimally invasive approach in all patients and there was no elective or emergency conversion to open procedure. There was no significant difference in the median operative time and blood loss between patients who underwent TD resection and preservation (Table 2). All patients were electively kept on ventilator support in the immediate postoperative period and extubated on the first postoperative day. The fluid requirement on the first postoperative day was slightly higher in the TD resection group although the difference was not statistically significant ($P = 0.059$). Patients in the TD resection had significantly higher pulse rate in the second postoperative day (111/min vs. 95/min, $P = 0.043$). There was no significant difference in the intraoperative fluid infusion, blood loss, urine output, mean blood pressure, pulse rate, postoperative urine output, and mean blood pressure between two groups. There was no postoperative mortality. Pneumonia was the most common complication in the postoperative period (Table 3). Anastomotic dehiscence was significantly higher in the TD-preserved group (58 vs. 10%, $P = 0.007$). One patient in TD-resected group had chylothorax due to slippage of clips that was managed successfully by thoracoscopic re-exploration and ligation.

The median (range) number of mediastinal lymph node count was similar in the TD-resected and TD-preserved groups [15(11–32) vs. 14(9–31), $P = 0.283$]. Histopathological examination of the resected specimen revealed complete pathological response (Becker's grade 1A) of the primary tumor in nine patients and grade IB response in three patients. Of the nine patients who had a complete pathological response of the primary tumor, three patients had evidence of tumor deposits in the regional lymph nodes. Pathological examination of the TD did not reveal evidence of tumor deposits in any of the patients.

Table 1 Demographic and clinicopathological parameters of patients with squamous cell carcinoma included in the study ($n = 22$)

Parameter	Value
Age (mean ± standard deviation) in years	54.6 ± 10.5
Sex (male:female)	10:12
BMI (mean ± standard deviation) in kg/m^2	18.5 ± 2.3
ECOG performance status, *n* (%)	
One	16 (72.7)
Two	6 (26.3)
Level of growth (mean ± standard deviation) in cm from incisors	29.1 ± 5.6
Grade of tumor, *n* (%)	
Well differentiated	9 (40.9)
Moderately differentiated	9 (40.9)
Poorly differentiated	4 (18.2)
Clinical T stage, *n* (%)	
T2	1 (4.6)
T3	18 (81.8)
T4	3 (13.6)
Clinical N stage, *n* (%)	
N0	13 (59.2)
N1	6 (27.2)
N2	3 (13.6)
Pathological T stage, *n* (%)	
T0	12 (54.5)
T2	4 (18.3)
T3	3 (13.6)
T4	3 (13.6)
Pathological N stage, *n* (%)	
N0	13 (59.1)
N1	9 (40.9)

ECOG Eastern Cooperative Oncology Group

Discussion

In the present series, patients who underwent TD resection had a relatively more hemodynamic change compared to TD-preserved patients though the difference was not statistically significant. Imamura et al. reported the development of early postoperative shock requiring massive fluid and plasma infusion in patients who underwent en bloc esophagectomy with TD resection [10]. However, with the restoration of relative intravascular hypovolemia, the hemodynamic state stabilized after 48 h. Dilatation of preexisting lymphatico-venous communications in the retroperitoneal region helps to restore intravascular volume [10]. In the current analysis, patients who underwent TD resection had a non-significant increased fluid requirement on the first postoperative day and significant tachycardia on the second postoperative day despite no significant difference in the blood loss between two groups. These changes suggest that TD resection results in intravascular hypovolemia secondary to a transient interruption in the return of fluid from the extravascular compartment. However, with appropriate fluid management, the transient hemodynamic changes do not adversely affect the postoperative recovery as evidenced by the absence of significant difference in the postoperative morbidity except for cervical anastomotic leak. Less incidence of anastomotic dehiscence in the TD-resected

Table 2 Comparison of perioperative hemodynamic parameters and fluid requirement in patients who underwent thoracic duct (TD) resection and preservation

Parameter	TD-excised group (*n* = 10)	TD-preserved group (*n* = 12)	*P* value
Operative time (median), min	427	440	0.460
Intraoperative fluid infusion (median), mL	3500	4650	0.107
Intraoperative blood loss, (median), mL	400	275	0.314
Intraoperative urine output, (median), mL	850	937.5	0.923
Intraoperative systolic blood pressure, (median), mmHg	118	116	1.000
Intraoperative diastolic blood pressure, (median), mmHg	77	76	0.674
Intraoperative pulse rate, (median), per min	91	100	0.123
POD 0 fluid infusion, (median), mL	1750	1630	0.539
POD 0 output, (median), mL	770	935	0.637
POD 0 systolic blood pressure, (median), mmHg	115	110	0.283
POD 0 diastolic blood pressure, (median), mmHg	82	76	0.036
POD 0 pulse rate, (median), per min	113	103	0.254
POD 1 fluid infusion, (median), mL	3310	2875	0.059
POD 1 output, (median), mL	1427	1634	0.722
POD 1 systolic blood pressure, (median), mmHg	119	110	0.093
POD 1 diastolic blood pressure, (median), mmHg	79	70	0.123
POD 1 pulse rate, (median), per min	114	94	0.050
POD 2 fluid infusion, (median), mL	2830	2690	0.346
POD 2 output, (median), mL	2055	1937	0.752
POD 2 systolic blood pressure, (median), mmHg	117	120	0.821
POD 2 diastolic blood pressure, (median), mmHg	80	75	0.180
POD 2 pulse rate, (median), per min	111	95	0.043

POD postoperative day

group could be due to the use of ischemic preconditioning of gastric conduit. Ischemic preconditioning by ligation of left gastric and short gastric vessels has been shown to reduce the anastomotic complications after esophagectomy [21]. Prophylactic ligation of TD during esophagectomy has been shown to reduce the incidence of chylothorax [22, 23]. In the present series, none of the patients in TD-preserved group had chylothorax. In contrast, one patient in the TD resection developed chylothorax requiring re-exploration and ligation. The occurrence of chyle leak secondary to slippage of the endoclips underscores the importance of secure ligation of TD to prevent postoperative chylothorax.

Lymph node involvement is an important prognostic factor in patients with esophageal cancer [1, 2]. However, the role of radical lymphadenectomy in esophageal cancer has been debated due to the absence of well-conducted randomized trials. Some investigators reported that surgery has reached its maximum therapeutic impact with limited lymphadenectomy, whereas others believe that aggressive surgery with an extended lymphadenectomy improves locoregional control and survival [3–6]. Most studies reported that improved lymph node retrieval is associated with improved survival. According to AJCC recommendation, an adequate lymphadenectomy in patients undergoing esophagectomy requires resection of 12 to 22 nodes [20]. With the advent of neoadjuvant chemoradiotherapy, there is a renewed controversy on the significance of lymphadenectomy as most of the studies showing improved survival with radical lymphadenectomy were done in patients undergoing surgery alone. A recent report from the CROSS-study group reported that the number of resected lymph nodes correlated with survival in patients undergoing surgery alone and not in patients who received neoadjuvant chemoradiotherapy [6]. A few other studies also questioned the therapeutic value of radical lymphadenectomy in patients receiving neoadjuvant chemoradiotherapy [24, 25]. However, the question that remains unanswered is when less radical lymphadenectomy is performed which group of lymph nodes are not resected. Studies have shown that lymphadenectomy along recurrent laryngeal group of nodes is associated with increased postoperative morbidity [3, 4]. However, recurrent laryngeal group of lymph nodes are frequently involved in patients with squamous cell carcinoma of the middle and lower thoracic esophagus [3, 4, 7]. In the present study, three patients who had a complete pathological response of the primary tumor after neoadjuvant chemoradiotherapy with the positive nodal disease had involvement of the left recurrent laryngeal group of lymph nodes. Miyata et al. reported that efficacy index of each lymph node station calculated by multiplying the incidence of lymph node metastasis with 3-year survival was not altered by neoadjuvant therapy suggesting that the therapeutic value of radical lymph node dissection was not

Table 3 Comparison of postoperative complications in patients who underwent thoracic duct (TD) resection and preservation

Parameter		TD-excised group ($n = 10$)	TD-preserved group ($n = 12$)	*P* value
Pneumonia, *n* (%)		8 (80%)	8 (66%)	0.481
Anastomotic dehiscence, *n* (%)	Absent	9 (90%)	5 (41.7%)	0.007
	Grade 1	0	2 (16.7%)	
	Grade 2	1 (10%)	4 (33.3%)	
	Grade 3	0	1 (8.3%)	
Conduit necrosis, *n* (%)	Absent	10 (100%)	11 (91.7%)	0.297
	Grade 1	0	0	
	Grade 2	0	1 (8.3%)	
	Grade 3	0	0	
Chyle leak, *n* (%)	Absent	9 (90%)	12 (100%)	0.292
	Grade 1	0	0	
	Grade 2	0	0	
	Grade 3	1 (10%)	0	
RLN palsy, *n* (%)	Absent	9 (90%)	8 (66.6%)	0.16
	Grade 1	1 (10%)	4 (33.3%)	
	Grade 2	0	0	
	Grade 3	0	0	

altered by neoadjuvant therapy [7]. The results of the present study and other reported series support the need for radical D2 lymphadenectomy in patients with esophageal cancer even in the setting of neoadjuvant chemoradiotherapy [26].

Udagawa et al. reported that resection of TD facilitates complete clearance of station 112 and 106 rec group of lymph nodes [11]. Recently Matsuda et al. in a retrospective analysis of 167 patients who underwent transthoracic esophagectomy with TD resection reported that TD resection improves mediastinal lymph node yield compared to TD preservation group [27]. However, the increased lymph node yield was not explained by TD resection alone as the number of paraesophageal lymph nodes was increased in the TD resection group. The authors have suggested that the use of a hybrid of the prone and left lateral decubitus positions for thoracoscopic transthoracic esophagectomy could have contributed to increased lymph node yield in addition to TD resection [27]. Also, the neoadjuvant treatment protocol was not standardized in the TD resection group. In the present series, there was no significant difference in the yield of mediational lymph nodes in patients who underwent resection of TD compared to TD preservation group. Tiny direct lymphatic communications were demonstrated between esophagus and TD [9]. However, the presence of tumor deposits in TD has not been systematically evaluated and reported. In the present series, examination of multiple sections of TD in the TD-resected group did not show evidence of tumor deposits. The mediastinal lymph node yield in the present series was less compared to a few Japanese series despite radical D2 lymphadenectomy [1, 2]. However, in the present series, all patients received neoadjuvant therapy. Studies have shown that neoadjuvant therapy decreases lymph node yield without influencing the therapeutic value of each lymph node station [7, 28]. The small sample size is the major limitation of the present study. However, the significance of TD excision in the era of neoadjuvant chemoradiotherapy has not been reported before and the results of the present study could guide future large prospective trials.

In conclusion, minimally invasive esophagectomy with TD duct resection results in transient hemodynamic disturbances in the immediate postoperative period, without adversely affecting postoperative recovery. In the setting of neoadjuvant chemoradiotherapy, TD resection does not improve lymph node yield.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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