Langenbeck's Archives of Surgery (2019) 404:335–341
https://doi.org/10.1007/s00423-019-01765-2

ORIGINAL ARTICLE

Anastomotic leakage following retrosternal pull-up

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Received: 21 September 2018 / Accepted: 13 February 2019 / Published online: 4 March 2019

Abstract

Purpose Narrow thoracic inlet might be associated with increased incidence of cervical anastomotic leakage (AL) after esophagectomy with retrosternal reconstruction. We retrospectively evaluated the relationship of the length from the suprasternal notch to the trachea (LST) and AL using computed tomography.

Methods In this retrospective study including 121 patients with esophageal cancer who underwent subtotal esophagectomy with retrosternal reconstruction between 2008 and 2016, clinicopathological characteristics, including the LST, surgical procedures, and perioperative outcomes, were compared between the AL and non-AL groups.

Results AL occurred in 19 of the 121 patients (15.7%). There were no associations between AL development and age, sex, body mass index, tumor location, TNM stage, histological type, surgical approach, or type of the anastomotic procedure. Surgery duration was longer in the AL group than in the non-AL group ($p = 0.004$). Other surgical factors such as intra-operative blood loss and anastomotic technique were not associated with AL. LST was significantly shorter in the AL group than in the non-AL group ($p < 0.001$). Multivariate analysis revealed that LST was a significant predictor of AL ($p < 0.001$).

Conclusion LST is a simple and useful predictor of AL after esophagectomy with retrosternal reconstruction.

Keywords Anastomotic leakage · Esophagectomy · Retrosternal route · Complication

Introduction

Surgical resection of the esophagus with en bloc lymphadenectomy is the cornerstone of curative treatment for patients with resectable esophageal cancer. However, esophagectomy is a highly invasive procedure with several serious complications. Anastomotic leakage (AL), along with pulmonary complications and recurrent nerve palsy, is one of the most frequent and serious complications of esophagectomy. Despite improvements in surgical techniques and perioperative care, the incidence of AL after esophagectomy has been reported to be between 13% and 30% [1–3]. AL is associated with not only prolonged fasting, hospitalization, and fatalities in the short term but also malnutrition and poor prognosis in the long term [4].

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The most common reconstruction after esophagectomy involves substitution with the stomach and is achieved via either the retrosternal or the posterior mediastinal route. Compared with the posterior mediastinal approach, retrosternal reconstruction offers several advantages, including decreased incidence of mediastinal abscess formation, reduced burden on the pulmonary system, prevention of tumor infiltration and local recurrence due to the orthotopic position, and ability to administer radiation therapy to tumor bed after esophagectomy with an associated reduction in recurrence risk. Therefore, one-third of patients with esophagectomy in Japan are treated via the retrosternal route [5]. However, reconstruction after esophagectomy using the retrosternal route necessitates the formation of an extra tunnel, and the gastric tube is inserted through the thoracic inlet and placed in the narrow space between sternum and trachea. A small Japanese study reported that size of the thoracic inlet, calculated by the inter-clavicular and sterno-bronchiocephalic distances, was associated with AL and anastomotic stenosis [6]. Therefore, we hypothesized that the anatomical location of the retrosternal space, especially the length from the suprasternal notch to the trachea (LST), might be associated with AL incidence after subtotal esophagectomy reconstruction by gastric tube via the retrosternal

route. We thus evaluated anatomical LST using axial computed tomography (CT) images and investigated its impact on AL incidence in patients with esophagectomy.

Materials and methods

This retrospective study included 172 patients with primary esophageal cancer and no distant organ metastases who underwent elective and potentially curative subtotal esophagectomy with reconstruction using cervical esophagogastric anastomosis via the retrosternal route at Nara Medical University Hospital in Nara, Japan, between January 2008 and December 2016. Patients with any of the following conditions were excluded: reconstruction by jejunum or colon ($n = 16$), anastomosis in locations other than the neck ($n = 16$), reconstruction by posterior mediastinal ($n = 5$) or antethoracic route ($n = 2$), cervical radiation for head and neck cancer before esophagectomy ($n = 3$), R2 macroscopic incomplete resection ($n = 4$), hand-sewn anastomosis for cervical esophageal cancer ($n = 3$), and hospital death due to respiratory failure without AL ($n = 2$). Therefore, a total of 121 patients were included in the final analysis. Written informed consent was obtained from all patients. This study was approved by the research ethics committee of Nara Medical University (No. 1734).

Esophageal cancer was staged according to the guidelines of the 7th edition of TNM Classification by the International Union against Cancer [7].

Surgery

Eligible patients underwent three-stage esophagectomy with thoracotomy or thoracoscopy with a two-field or three-field lymphadenectomy. The thoracic procedure was performed from the right thorax using either thoracotomy or thoracoscopy in the left decubitus position. All patients underwent cervical esophagogastric anastomosis. A narrow gastric tube with a width of 3–4 cm was created by laparotomy or laparoscopy, using a linear stapler along the greater curvature of the stomach. The staple line was then covered with seromuscular sutures. Pyloromyotomy was not performed routinely. Retrosternal tunnel was created by blunt finger dissection and a long delicately curved intestinal retractor during open laparotomy or by laparoscopic monopolar or the LigaSure vessel sealing system (Valley lab, Boulder, CO) during laparoscopy.

Esophagogastrostomy was performed with end-to-side anastomosis on the greater curvature of the gastric tube using a circular stapler between 2008 and 2012 and end-to-end anastomosis with triangulating anastomosis using a linear stapler between 2013 and 2016 [8]. The switch to the triangulating anastomosis was made because the circular stapler method showed the high rate of anastomotic stenosis.

The circular stapler method was performed by a 21- or 25-mm circular stapling device. The circular stapler was inserted into the tip of the gastric tube, and anastomosis was created at the greater curvature wall in the gastric tube about 5 cm from the distal end of the gastric tube. The triangular stapling technique was described previously [8]. Briefly, after three or four suspension sutures were made to secure the anastomosis, the first instrumental anastomosis was applied to the posterior wall of the remnant esophagus and the gastric conduit in an inverted fashion. To create the anterior wall of the anastomosis, the second and third anastomoses were performed using two additional linear staples in an extroverted fashion.

Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy was administered to patients with cStage IB–III esophageal cancer. Standard regimen for neo-adjuvant chemotherapy included only chemotherapy with two courses of docetaxel, cisplatin, and 5-fluorouracil. The regimen comprised 35 mg/m^2 of docetaxel on day 1 and 6 mg/m^2 of cisplatin and 350 mg/m^2 of 5-fluorouracil from days 1 to 5.

Measurement of LST

Preoperative thoracic CT images of all patients were reviewed. The top of the sternum and the trachea were identified on the same axial CT image to measure LST (Fig. 1). Furthermore, the length from the suprasternal notch to the vertebral body (LSV) was measured to assess the complete thoracic inlet. To evaluate the sensitivity and specificity for its association with AL, the receiver operating characteristic (ROC) curve was calculated, and the Youden index was estimated to determine optimal cutoff LST value.

Definition of AL

AL was defined according to the following criteria: presence of skin redness, edema, or discharge of saliva, gastric juice, or pus from the cervical wound or drain; confirmation of extravasation of the contrast medium from the anastomotic site or staple line by esophagogram; and/or identification of abscess formation around the anastomotic site by CT.

Statistical analysis

Qualitative data were compared using the chi-square test or Fisher's exact test, and continuous variables presented as means were compared using Student's t test. Multivariate logistic regression analysis was performed including variables that were significant in univariate analysis with a p value <

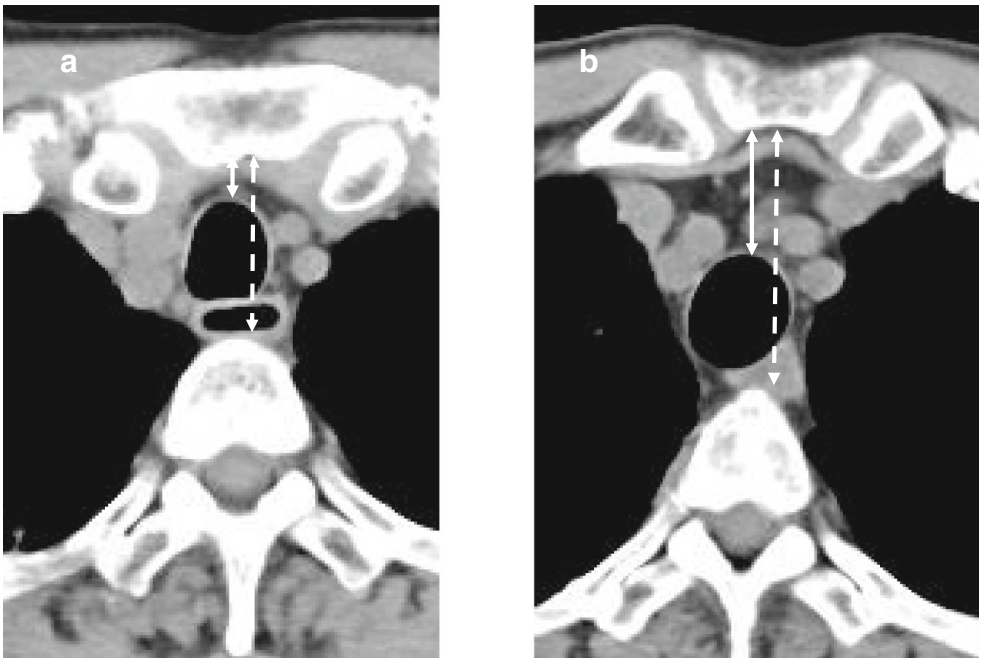

Fig. 1 Measurement of the length from suprasternal notch to the trachea (LST) (solid arrow) and the length from suprasternal notch to the vertebral body (LSV) (dotted arrow). Axial computed tomography (CT) images of (**a**) a patient with a narrow LST of 6 mm, LSV 39 mm and (**b**) a patient with a wide LST of 33 mm, LSV of 64 mm

0.15, anastomotic technique, and well-known risk factors for AL, such as diabetes mellitus or cardiovascular disease. For all tests, a p value < 0.05 was considered significant. All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, NC).

Results

AL

Patient characteristics are shown in Table 1. AL occurred in 19 patients (15.7%) on a median of eight days after surgery. Treatment of AL consisted of antibiotics and nil-by-mouth in four patients, drainage under local anesthesia in ten patients, and drainage under general anesthesia in three patients. There were no in-hospital deaths due to AL in this study cohort.

Risk factors for AL

Clinical factors such as age, sex, coexisting disease, and tumor location were not associated with AL. Surgery duration was longer in the AL group than in the non-AL group ($p = 0.004$). Intra-operative blood loss was not associated with AL. The AL rate was higher in the circular stapling technique (20.0%) than in the triangular stapling technique (11.4%). However, these differences were not statistically significant ($p = 0.198$). In the circular stapling group, one of the seven patients (14.3%) using 21-mm circular stapling device had AL and 11 of 53 patients (20.8%) using 25-mm circular stapling device had AL. There were no significant differences between stapler sizes ($p = 0.688$). LST in the AL group was significantly shorter than that in the non-AL group ($p < 0.001$). However, LSV was not found to be associated with AL ($p = 0.205$).

To evaluate the relationships between AL and clinical factors, variables with a $p < 0.15$ in Table 1, anastomotic technique, and well-known risk factors for AL, such as diabetes mellitus or cardiovascular disease, were included in multivariate logistic analysis, which revealed that LST was an independent risk factor for AL ($p < 0.001$, Table 2).

ROC analysis

Using AL incidence as the endpoint, the area under the ROC curve for LST was 0.924 (95% confidence interval 0.871–0.978). The Youden index was maximal for an LST value of 18 mm, with a sensitivity of 95.0% and a specificity of 76.0%. Therefore, the cutoff value for LST was set at 18 mm.

Relationship between LST and clinical and perioperative variables

Finally, we analyzed the relationship between LST and clinical and perioperative variables (Table 3). Although LST was not associated with body length and BMI, it was strongly associated with LSV ($p < 0.001$). Furthermore, the rate of older patients ($p = 0.030$) and coexisting diabetes mellitus ($p = 0.039$) were higher among those with an LST < 18 mm than those with an LST ≥ 18 mm. The rates of endoscopic dilatation due to anastomotic stenosis were similar between LST < 18 mm and LST ≥ 18 mm groups ($p = 0.549$).

Table 1 Relationship between patient characteristics and anastomotic leakage

Characteristics	Leakage ($n = 19$)	No Leakage ($n = 102$)	p value
Sex			
Male	17 (89.5%)	83 (81.4%)	0.392
Female	2 (10.5%)	19 (18.6%)	
Age (years)	65.4 ± 7.4	64.7 ± 10.8	0.685
Body mass index (kg/m^2)	22.6 ± 3.3	21.4 ± 3.2	0.120
Coexisting condition			
Cardiovascular disease	10 (52.6%)	39 (38.2%)	0.241
Pulmonary disease	0 (0%)	9 (7.4%)	0.178
Diabetes	3 (15.8%)	14 (13.7%)	0.812
Smoking at time of diagnosis	7 (36.8%)	46 (45.1%)	0.505
Tumor location			0.877
Upper	2 (10.5%)	12 (11.8%)	
Middle or lower	17 (85.5%)	90 (88.2%)	
Neo-adjuvant chemotherapy	12 (63.2%)	66 (66.0%)	0.811
Tumor size (mm)	32.3 ± 11.9	35.1 ± 22.7	0.625
Depth of tumor invasion			0.833
T0–1	10 (52.6%)	51 (50.0%)	
T2–4	9 (47.4%)	51 (50.0%)	
Lymph node metastasis			0.236
N0	11 (57.9%)	44 (43.1%)	
N1–3	8 (42.1%)	58 (56.9%)	
Stage			0.462
I	7 (62.5%)	29 (62.8%)	
II–IV	12 (25.0%)	73 (15.3%)	
Histological type			0.239
Squamous cell carcinoma	19 (100.0%)	95 (93.1%)	
Adenocarcinoma	0 (0.0%)	7 (6.9%)	
Thoracoscopy	17 (89.5%)	92 (92.9%)	0.603
Laparoscopy	12 (63.2%)	57 (57.6%)	0.651
Duration of surgery	621 ± 84	562 ± 80	0.004
Operative blood loss (ml)	533 ± 514	402 ± 289	0.117
Anastomotic technique			0.198
Circular stapling	12 (63.2%)	48 (47.1%)	
Triangular stapling	7 (36.8%)	54 (52.9%)	
LST (mm)	12.9 ± 3.4	21.6 ± 5.0	< 0.001
LSV (mm)	48.5 ± 6.7	50.7 ± 7.0	0.205

Data are presented as numbers (%) or means ± standard deviation

LST length from the suprasternal notch to the trachea

LSV length from the suprasternal notch and the vertebral body

Discussion

Although advances in surgical techniques and perioperative management have made it possible to safely perform esophagectomy, AL remains a common and bothersome complication. Previous studies have reported several risk factors of AL after esophagectomy, such as diabetes mellitus, cardiovascular disease, active smoking, obesity, and anastomotic techniques [9–13]. However, it is difficult to preoperatively manage such risk factors based on just patient background.

During retrosternal reconstruction, surgeons occasionally experience certain difficulties in passing the gastric tube through the retrosternal space if the space surrounding the manubrium and trachea is narrow. We hypothesized that such narrow retrosternal space might be associated with AL incidence after subtotal esophagectomy reconstructed by the gastric tube via the retrosternal route. Thus, we reviewed LST using CT imaging in our own cases with subtotal esophagectomy. We observed that short LST, an indicator for the narrow retrosternal space, was an independent risk factor for AL. To the best of our knowledge, this is the first study to demonstrate that LST as an indicator of the anatomical size of the thoracic inlet has a significant impact on AL.

One potential cause of the association between LST and AL is that the gastric tube tip placed in the retrosternal space might be compressed by the trachea and the sternum, leading to poor peripheral blood perfusion of the gastric tube. Mechanical stress on the gastric tube might be higher with gastric pull-up via the retrosternal route than with the posterior mediastinal route. Anegg et al. reported that the oxygen supply with retrosternal reconstruction was worse than that with posterior mediastinal reconstruction [14]. In addition, the sternoclavicular joint might impinge on the gastric tube reconstructed via the retrosternal route. Therefore, a small retrosternal space might lead to the deterioration of blood flow at the cervical anastomosis.

Whether the best route for reconstruction after esophagectomy is the retrosternal or the posterior mediastinal approach remains controversial. The posterior mediastinal route is preferred by many surgeons due to lower rates of cardiopulmonary complications, AL, and hospital mortality [15–18]. In contrast, retrosternal reconstruction was reported to be associated with a lower rate of postoperative pneumonia [19]. However, a meta-analysis by Urschel et al. revealed that the choice of the reconstruction route was not associated with the incidence of postoperative morbidity or mortality [20]. Several studies have shown that anatomical factors might also affect the risk of AL in both reconstruction approaches. In retrosternal reconstruction, Kunisaki et al. reported that the size of the thoracic inlet space (TIS) calculated by the inter-clavicular and sterno-bronchiocephalic distances was associated with AL and anastomotic stenosis [6]. We also evaluated the relationship between the TIS and LST; TIS in the LST < 18 mm and LST ≥ 18 mm were 303 ± 103 mm^2 and 287 ± 89 mm^2, respectively. There were no significant differences between the width and narrowness in the LST groups ($p = 0.382$). Furthermore, a recent Japanese study reported that the size of the superior thoracic aperture was associated with AL. Particularly, they reported that the relationship between AL and the size of the superior thoracic aperture was stronger with the posterior mediastinal route

Table 2 Multivariate regression analysis for the prediction of anastomotic leakage

Variable	OR	95% CI	*p* value
BMI	1.307	0.999–1.774	0.051
Cardiovascular disease (yes vs no)	2.349	0.443–15.502	0.330
Diabetes (yes vs no)	0.158	0.009–1.547	0.119
Duration of surgery	1.007	0.997–1.018	0.699
Operative blood loss	0.999	0.997–1.003	0.699
Anastomotic technique (circular vs triangle)	4.975	0.924–32.650	0.617
LST	0.598	0.456–0.726	< 0.001

BMI body mass index, *LST* length from the suprasternal notch to the trachea, *OR* odds ratio, *CI* confidence interval

than with the retrosternal route [21]. Therefore, the anatomical size of the thoracic inlet is likely to be associated with AL at the cervical anastomosis in patients who undergo reconstruction after subtotal esophagectomy not only via the retrosternal route but also the posterior mediastinal route.

Table 3 Relationship between the LST and the clinical and perioperative variables

Characteristics	LST < 18 mm ($n = 38$)	LST ≥ 18 mm ($n = 83$)	*p* value
Sex			
Male	34 (89.5%)	66 (79.5%)	0.180
Female	4 (10.5%)	17 (20.5%)	
Age	66.8 ± 6.7	63.9 ± 6.7	0.030
Body length (cm)	164.3 ± 5.5	164.3 ± 6.4	0.958
BMI (kg/m^2)	21.4 ± 3.4	21.6 ± 3.1	0.804
LSV (mm)	47.1 ± 6.5	51.9 ± 6.7	< 0.001
Coexisting condition			
Cardiovascular disease	20 (52.6%)	29 (34.9%)	0.066
Pulmonary disease	0 (0%)	9 (7.4%)	0.035
Diabetes	9 (23.7%)	8 (9.6%)	0.039
Smoking at the diagnosis	18 (47.4%)	35 (42.2%)	0.593
Tumor location			0.712
Upper	5 (13.2%)	9 (10.8%)	
Middle or lower	33 (86.8%)	74 (89.2%)	
Neo-adjuvant chemotherapy	12 (63.2%)	66 (66.0%)	0.811
Tumor size (mm)	36.4 ± 20.3	33.9 ± 21.9	0.563
Depth of tumor invasion			0.650
T0–1	18 (47.4%)	43 (51.8%)	
T2–4	20 (52.6%)	40 (48.2%)	
Lymph node metastasis			0.371
N0	15 (57.9%)	43 (51.8%)	
N1–3	23 (42.1%)	40 (48.2%)	
Stage			0.576
I	10 (26.3%)	26 (31.3%)	
II–IV	28 (73.7%)	57 (68.7%)	
Histological type			0.868
Squamous cell carcinoma	36 (94.7%)	78 (94.0%)	
Adenocarcinoma	2 (5.3%)	5 (6.0%)	
Thoracoscopy	35 (94.6%)	74 (90.2%)	0.603
Laparoscopy	25 (67.6%)	44 (53.7%)	0.651
Duration of surgery	590 ± 77	562 ± 85	0.089
Operative blood loss (ml)	402 ± 420	432 ± 290	0.651
Anastomotic stenosis	14 (36.8%)	26 (31.3%)	0.549

Data are presented as numbers (%) or means ± standard deviation

LST length from the suprasternal notch and the trachea

LSV length from the suprasternal notch and the vertebral body

Route of reconstruction can be changed to intrathoracic, posterior mediastinal, or antethoracic anastomosis to reduce the rate of AL in patients with a short LST. To switch to the posterior mediastinal route is an alternative option for cervical anastomosis after subtotal esophagectomy. However, our study also showed that narrow LST is associated with LSV. Therefore, it is unclear whether switching the reconstruction route can reduce AL because narrow thoracic inlet is reported to be associated with AL after posterior mediastinal reconstruction [21]. The rate of AL was reported to be higher with cervical anastomosis than with thoracic anastomosis [10, 22]. In Western countries, surgeons prefer Ivor Lewis esophagectomy with intrathoracic anastomosis for esophageal adenocarcinoma in contrast to Japan, where subtotal esophagectomy with three-field lymphadenectomy and cervical anastomosis is widely used for esophageal squamous cell carcinoma. However, surgeons might hesitate to use thoracic anastomosis for tumors located in the upper thoracic esophagus. An alternative to reduce the AL rate in patients with a short LST is to resect a portion of the manubrium, the associated costal cartilage, and the medial portion of the left clavicle, to expand the TIS and avoid compression of the gastric tube [23, 24]. This approach, albeit favored by some expert surgeons, has not been utilized widely. Accurate risk assessment of AL after esophagectomy might help improve intra-operative and post-operative patient care.

Another factor related to AL was the long duration of operation. Therefore, we examined the reasons for the long duration of operation. Patients who underwent an operation for a duration longer than 570 min, which is median operation time, had higher BMI than patients who underwent an operation for a duration lesser than 570 min. A Japanese nationwide survey reported that the duration of operation for patients with high BMI was longer than those with low BMI [25]. However, in this study we have not reported regarding the other factors which may make esophagectomy challenging, such as tumor size, tumor invasion, or lymph node metastases.

The current study has several limitations that should be addressed. First, this was a relatively small retrospective study with a potential historical bias. Further prospective studies are needed with larger number of patients. Second, blood flow of

the gastric tube was not evaluated. Intra-operative blood flow assessment with indocyanine green fluorescence angiography was reported as useful in detecting perfusion of the gastric tube [26, 27]. Recognition of a reduction in blood perfusion of the gastric tube before and after going through the TIS should facilitate implementation of countermeasures such as a change in the reconstruction route. Third, LST might change with inspiration and expiration, body position, or the cervical spine abnormalities such as kyphosis. However, patients stretch their neck and breathe in and stop when CT is performed at our hospital.

Conclusion

Short LST was a significant risk factor for AL after subtotal esophagectomy reconstructed using the gastric tube via the retrosternal route. Therefore, LST should be preoperatively evaluated for optimal patient care and surgical treatment strategy.

Authors' contributions Study conception and design: Matsumoto, Sho. Acquisition of data: Matsumoto, Wakatsuki, Migita, Miyao. Analysis and interpretation of data: Matsumoto, Nakade, and Kunishige. Drafting of manuscript: Matsumoto, Sho. Critical revision of manuscript: Matsumoto, Sho.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was conducted with the approval of the Nara Medical University Hospital Institutional Review Board (No. 1734).

Informed consent Informed consent was obtained from all individual participants included in the study.

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