Original Article

Morphomic predictors for post-esophagectomy pulmonary complications and overall survival

Chien-Hung Chiu[1], Peng Zhang[2], Jules Lin[3], Andrew C. Chang[3], Brian E. Ross[2], Binu Enchakalody[2], Nidhi V. Shah[2], Yun-Hen Liu[1], Yin-Kai Chao[1], Stewart C. Wang[2]

[1]Division of Thoracic Surgery, Chang Gung Memorial Hospital at Linkou, Taoyuan; [2]Department of Surgery, University of Michigan, Ann Arbor, MI, USA; [3]Section of Thoracic Surgery, University of Michigan, Ann Arbor, MI, USA

Contributions: (I) Conception and design: CH Chiu, J Lin, AC Chang, YH Liu, YK Chao, SC Wang; (II) Administrative support: AC Chang, YK Chao, SC Wang; (III) Provision of study materials or patients: CH Chiu, J Lin, YH Liu, YK Chao, SC Wang; (IV) Collection and assembly of data: CH Chiu, P Zhang, BE Ross, B Enchakalody, NV Shah; (V) Data analysis and interpretation: CH Chiu, J Lin, P Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Stewart C. Wang, MD, PhD. Department of Surgery, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA. Email: stewartw@med.umich.edu.

Background: Esophagectomy following neoadjuvant chemoradiotherapy (nCRT) is a curative treatment for locally advanced esophageal cancer. However, pulmonary complications are the most common postoperative issues and can adversely affect survival. While numerous studies have investigated predictors for these complications and survival, morphomic predictors, derived from body composition measurements on computed tomography scans, have been rarely reported. Our study aims to delineate morphomic predictors for post-esophagectomy pulmonary complications and overall survival.

Methods: We retrospectively analyzed esophageal cancer patients who received nCRT followed by esophagectomy between 2004 and 2016. Preoperative clinical and morphomic variables were collected to evaluate post-esophagectomy pulmonary complications and overall survival. Multivariable logistic regression and Cox's proportional hazard model were used for analysis.

Results: The study involved 221 esophageal cancer patients who received nCRT followed by surgery. Factors such as increased blood loss (P=0.01), more harvested nodes (P<0.001), advanced pT stage (P=0.01), elevated visceral adipose tissue (VAT) density (P=0.04), and reduced skeletal muscle (SM) area (P=0.01) were linked to pulmonary complications. Additionally, being male (P=0.01), increased blood loss (P<0.001), non-R0 resection margin (P=0.001), advanced pStage (P<0.001), advanced pT stage (P=0.02), and decreased SM density (P=0.045) were associated with poorer overall survival.

Conclusions: Increased VAT density and decreased SM area were associated with pulmonary complications, while decreased SM density was linked to poorer overall survival. Preoperative analytic morphomics aids in predicting both postoperative pulmonary complications and survival.

Keywords: Esophageal cancer; esophagectomy; analytic morphomics; pulmonary complications; survival

Submitted Aug 01, 2024. Accepted for publication Nov 29, 2024. Published online Jan 22, 2025.
doi: 10.21037/jtd-24-1227
View this article at: https://dx.doi.org/10.21037/jtd-24-1227

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy yields favorable long-term survival for locally advanced esophageal cancer, especially for esophageal squamous cell carcinoma (ESCC) (1). Despite advancements in surgical techniques, anesthesia, and perioperative care, pulmonary complications remain common and are a leading cause of hospital mortality after esophagectomy (2-9). Additionally, while these complications negatively affect perioperative outcomes, their impact on long-term survival remains unclear (3,4,8,10-14).

The prognosis of esophageal cancer is heavily influenced by the tumor stage at the time of initial diagnosis (15). For patients undergoing surgery, the pathological stage appears to have greater prognostic value than the clinical stage (16,17). In addition to tumor characteristics, various clinical variables—including patient-related and treatment-related factors—also impact the survival of esophageal cancer (4,10,15-17).

Analytic morphomics, which extracts body composition information from computed tomography (CT), offers an objective assessment of an individual's functional and nutritional status. These personalized morphomic measures have been linked to short-term surgical outcomes and survival in malignant diseases (18,19). However, research on morphomic predictors for post-esophagectomy complications and survival, especially for patients undergoing nCRT, is limited.

Highlight box

Key findings

- Increased visceral adipose tissue (VAT) density and decreased skeletal muscle (SM) area were identified as significant predictors of post-esophagectomy pulmonary complications.
- Decreased SM density was associated with poorer overall survival.

What is known and what is new?

- Esophagectomy following neoadjuvant chemoradiotherapy is a curative treatment for locally advanced esophageal cancer, but pulmonary complications are common postoperative issues that negatively impact survival.
- The present study investigates morphomic predictors, specifically derived from body composition measurements on computed tomography (CT) scans, delineating the association between increased VAT density, decreased SM area, and post-esophagectomy pulmonary complications, while also highlighting the link between decreased SM density and poorer overall survival.

What is the implication, and what should change now?

- Preoperative analytic morphomics can be a valuable tool in predicting both postoperative pulmonary complications and overall survival in esophageal cancer patients after esophagectomy, as identifying patients with increased VAT density and decreased SM area preoperatively can help tailor perioperative care to mitigate risks.
- Implement routine morphomic analysis using preoperative CT scans to better assess and manage the risk factors for pulmonary complications and overall survival, and develop targeted prehabilitation programs to improve SM density and optimize VAT density before surgery, potentially improving patient outcomes.

In this retrospective study, we aimed to identify clinical and morphomic factors linked to pulmonary complications and survival after esophagectomy in ESCC patients following nCRT. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1227/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201701548B0) on December 26, 2017 and individual consent for this retrospective analysis was waived. A total of 276 ESCC patients underwent esophagectomy following nCRT at Chang Gung Memorial Hospital (Taoyuan) between August 2004 and December 2016. After excluding patients with unavailable CT scans or pathological reports, 221 patients were included in this study.

All patients diagnosed with ESCC underwent biopsies, endoscopic ultrasound, CT scans, and positron emission tomography for comprehensive staging. The cancer staging system utilized was the Eighth Edition of the American Joint Committee on Cancer Staging Manual. The last follow-up date for this study was in August 2020.

nCRT

The chemotherapy regimens for nCRT included cisplatin with 5-fluorouracil or carboplatin with paclitaxel. The radiation dose administered during nCRT ranged from 3,000 to 5,600 cGy (20). Restaging occurred 4 to 6 weeks post-nCRT, followed by esophagectomy 6 to 8 weeks later.

Surgery

The thoracic procedure was conducted with the patient placed specifically in the semiprone position, a crucial aspect that has been thoroughly described in previous detailed reports (21). Upper esophageal tumors underwent the McKeown procedure, and middle or lower lesions the Ivor Lewis procedure. Surgical approaches included open, minimally invasive, or hybrid surgery. Suspected cervical nodal disease required 3-field lymph node dissection; otherwise, 2-field dissection was performed.

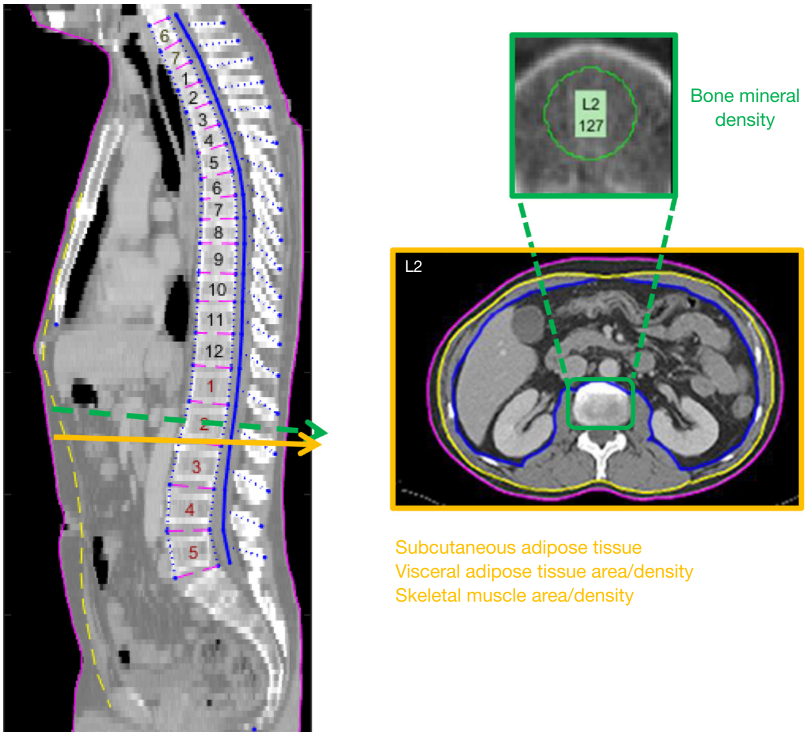

Figure 1 Bone mineral density was measured within trabecular bone at the mid-L2 level (yellow arrow), while other morphomic variables were assessed at the bottom of L2 (green dotted arrow). Subcutaneous adipose tissue area represented the total area of fat-intensity pixels between the fascia (yellow line) and skin (purple line). Visceral adipose tissue area encompassed the total area of fat-intensity pixels within the visceral cavity. Visceral adipose tissue density indicated the median pixel intensity of fat-intensity pixels in these areas. Skeletal muscle area denoted the total area of muscle-intensity pixels between the muscle wall and fascia boundaries (blue and yellow lines). Skeletal muscle density reflected the median pixel intensity of muscle-intensity pixels in these areas.

Analytic morphomics

Analytic morphomics processing was conducted following previously described methods (20,22). All CT scans were semi-automatically processed using algorithms in MATLAB R2016b (The MathWorks, Inc., Natick, MA, USA). Morphomic variables were analyzed at the cross-sectional level of the bottom of the secondary lumbar vertebra (L2), excluding bone mineral density (BMD). The specific analytic morphomics were as follows (*Figure 1*):

(I) BMD: average pixel intensity [Hounsfield units (HU)] within trabecular bone of vertebra at mid-L2 level.
(II) Subcutaneous adipose tissue (SAT) area: area of fat-intensity pixels (−205 to −51 HU) between the fascia and skin.
(III) Visceral adipose tissue (VAT) area: area of fat-intensity pixels within the fascial envelope.
(IV) VAT density: median pixel intensity of fat-intensity pixels in VAT area.
(V) Skeletal muscle (SM) area: area of muscle-intensity pixels (−29 to 150 HU) between the muscle wall and fascia boundaries.
(VI) SM density: median pixel intensity of muscle-intensity pixels in SM area.

Statistical analysis

Categorical variables were summarized using counts and percentages, while continuous variables were presented as means and standard deviations. Univariate analysis compared differences between patients with and without postoperative pulmonary complications. The Fisher exact test compared categorical variables, while the two-sample *t*-test compared continuous variables. Survival probabilities were estimated using the Kaplan-Meier estimator, and differences among risk groups were evaluated using the logrank test.

Multivariable logistic regression and Cox proportional hazards models were employed for binary and time-to-event mortality outcomes, respectively. Odds ratios and hazard ratios, along with their associated P values, were reported. Both odds ratios and hazard ratios correspond to a one standard deviation change in terms of individual morphomic variables. Model selection based on the Akaike information criterion yielded the best models. Statistical analyses were conducted using R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) (23).

Postoperative care and follow-up

After surgery, patients moved to the intensive care unit and were extubated. Discharge criteria included returning to normal activities and tolerating a semiliquid diet. Postoperative hospital stay duration was measured from surgery to discharge.

Pulmonary complications were defined as follows: pneumonia; pleural effusion or pneumothorax requiring intervention; respiratory failure necessitating reintubation; atelectasis with mucous plugging necessitating bronchoscopy; acute aspiration; acute respiratory distress syndrome; tracheobronchial injury; and prolonged intubation (exceeding 72 hours) (24). The severity of these complications was assessed using the Clavien-Dindo classification system (25).

Postoperative adjuvant therapy was administered to patients with non-R0 resection or recurrence risk factors (26). Postoperative surveillance entailed CT scans every 6 months for the initial 2 years, followed by annual scans thereafter. Survival data were updated every 6 months using the Taiwan Cancer Registry Database (https://twcr.tw/). Overall survival was defined as the duration from surgery to death, with censoring at the date of the last follow-up.

Results

Of the 221 patients, 80 (36.2%) experienced at least one pulmonary complication following esophagectomy. The majority of patients were male (95.9%), with a mean age of 54.2 years. Those with pulmonary complications had longer intensive care unit stays (8 *vs.* 2 days, P<0.001), extended hospital stays (42 *vs.* 26 days, P<0.001), and higher hospital mortality (15% *vs.* 0.7%, P<0.001) (*Table 1* and Table S1). The incidence and severity of pulmonary complications were detailed in *Table 2*, which showed that pleural effusion was the most common complication (80.0%), followed by pneumonia (42.5%) and respiratory failure (18.8%).

There were no significant differences between patients with or without pulmonary complications in traditional

Table 1 Demographic, clinical, and morphomic factors

Variables	Overall (n=221)	Pulmonary complications		P value
		No (n=141)	Yes (n=80)	
Age (years)	54.2±8.8	53.7±8.7	55.2±9.1	0.24
Gender				0.29
Male	212 (95.9)	137 (97.2)	75 (93.8)	
Female	9 (4.1)	4 (2.8)	5 (6.3)	
Body weight (kg)	60.1±10.9	60.9±11	58.7±10.7	0.14
Body mass index (kg/m^2)	22±3.6	22.2±3.7	21.6±3.5	0.20
Albumin (g/dL)	4.1±0.4	4.1±0.4	4.1±0.4	0.96
Charlson comorbidity index				0.50
0	126 (57)	79 (56.0)	47 (58.8)	
1	45 (20.4)	32 (22.7)	13 (16.3)	
2	36 (16.3)	23 (16.3)	13 (16.3)	
>2	14 (6.3)	7 (5.0)	7 (8.8)	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Overall (n=221)	Pulmonary complications		P value
		No (n=141)	Yes (n=80)	
Bone mineral density (HU)	167.7±60.5	171.1±58.6	161.7±63.8	0.28
Subcutaneous adipose tissue				
Area (mm^2)	5,110±3,703	5,217±3,850	4,921±3,443	0.56
Visceral adipose tissue				
Area (mm^2)	7,970±6,068	7,891±5,601	8,107±6,849	0.81
Density (HU)	−91.4±9.4	−92.1±9.2	−90.2±9.5	0.15
Skeletal muscle				
Area (mm^2)	11,802±1,915	12,065±1,912	11,339±1,843	0.006
Density (HU)	50.2±7.1	50.8±6.4	49.1±8.2	0.12
Type of surgery				0.76
Open + hybrid	153 (69.2)	99 (70.2)	54 (67.5)	
Minimally invasive surgery	68 (30.8)	42 (29.8)	26 (32.5)	
Surgery procedure				0.03
McKeown	102 (46.2)	57 (40.4)	45 (56.3)	
Ivor-Lewis	119 (53.8)	84 (59.6)	35 (43.8)	
Quality of resection				0.12
R0	174 (78.7)	116 (82.3)	58 (72.5)	
R1 + R2	47 (21.3)	25 (17.7)	22 (27.5)	
Blood loss (mL)	249±398	186±187	361±599	0.01
Number of nodes harvested	18±12	16±11	21±14	0.003
pStage				0.08
Early (0 + I + II)	141 (63.8)	96 (68.1)	45 (56.3)	
Late (III + IV)	80 (36.2)	45 (31.9)	35 (43.8)	
pT				<0.001
Early (0 + I + II)	100 (45.2)	76 (53.9)	24 (30.0)	
Late (III + IV)	121 (54.8)	65 (46.1)	56 (70.0)	
pN				0.23
Negative (0)	153 (69.2)	102 (72.3)	51 (63.8)	
Positive (I + II + III)	68 (30.8)	39 (27.7)	29 (36.3)	
Intensive care unit duration (days)	4±9.8	2±1.3	8±15.5	<0.001
Postoperative hospital stay (days)	31±23.3	26±9.0	42±34.7	<0.001
Hospital mortality	13 (5.9)	1 (0.7)	12 (15.0)	<0.001

Categorical data are shown as n (%). Continuous data are expressed as mean ± standard deviation. HU, Hounsfield units.

Table 2 Incidence and severity of pulmonary complications

Variable	Number (%)
Pneumonia	34 (42.5)
Pleural effusion†	64 (80.0)
Pneumothorax†	2 (2.5)
Respiratory failure‡	15 (18.8)
Atelectasis§	2 (2.5)
Acute aspiration	4 (5)
Acute respiratory distress syndrome	6 (7.5)
Tracheobronchial injury	0
Prolonged intubation¶	13 (16.3)
Clavien-Dindo classification	
Grade 1	2 (2.5)
Grade 2	10 (12.5)
Grade 3	51 (63.8)
Grade 4	5 (6.3)
Grade 5	13 (16.3)

†, events requiring intervention for drainage; ‡, events requiring reintubation; §, events requiring bronchoscopy; ¶, defined as intubation more than 72 hours.

Table 3 Multivariable logistic regression with parsimonious model after stepwise variable selection for pulmonary complications

Predictors	Parsimonious model	
	OR (95% CI)	P value
Blood loss	1.002 (1.0004–1.003)	0.01
Number of nodes harvested	1.05 (1.02–1.08)	<0.001
Albumin	1.86 (0.81–4.27)	0.14
Late pT (III + IV)	2.50 (1.33–4.72)	0.005
Visceral adipose tissue density†	1.4 (1.01–1.94)	0.04
Skeletal muscle area†	0.64 (0.46–0.9)	0.009
Skeletal muscle density†	0.73 (0.52–1.01)	0.06

†, OR corresponds to one standard deviation change in terms of individual variables. OR, odds ratio; CI, confidence interval.

nutritional factors such as body weight, body mass index, and serum albumin levels. Regarding surgical and pathological factors, McKeown procedure (P=0.03), higher blood loss (P=0.01), more harvested nodes (P=0.003), and advanced pT stage (P<0.001) were associated with the incidence of pulmonary complications. Concerning morphomic factors, decreased SM area (P=0.006) was correlated with the incidence of pulmonary complications (*Table 1*). In the multivariable Cox regression model, increased blood loss (P=0.01), more harvested nodes (P<0.001), advanced pT stage (P=0.005), elevated VAT density (P=0.04), and decreased SM area (P=0.009) were associated with pulmonary complications (*Table 3*).

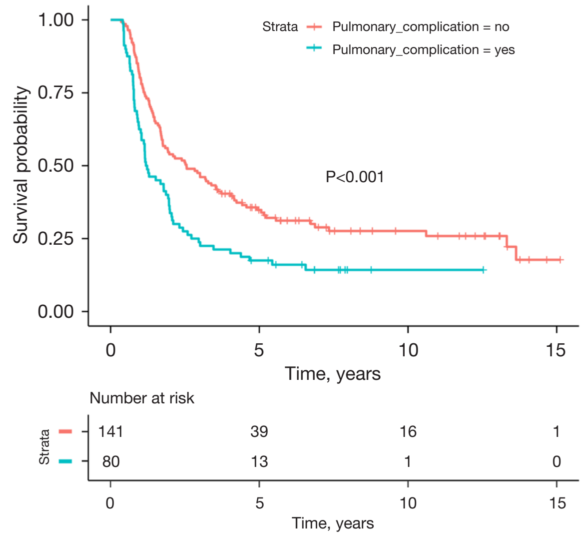

Figure 2 Overall survival in patients with and without postoperative pulmonary complications with confidence limits and patients at risk over time.

Overall survival outcomes

The median follow-up time was 7.7 years, with a median overall survival of 1.9 years. The 1-, 3-, and 5-year overall survival probabilities were 74%, 39%, and 29%, respectively. Patients with pulmonary complications exhibited a shorter median overall survival (1.2 *vs.* 2.6 years) and lower survival probabilities (1 year: 63% *vs.* 80%; 3 years: 24% *vs.* 48%; 5 years: 18% *vs.* 35%) (*Figure 2*) (P<0.001).

In univariate analysis, factors such as increased blood loss, non-R0 resection margin, advanced pStage, advanced pT stage, and positive pN were associated with poorer overall survival. In multivariate analysis, being male (P=0.01), increased blood loss (P<0.001), non-R0 resection margin (P=0.001), advanced pStage (P<0.001), advanced pT stage (P=0.02), and decreased SM density (P=0.045) were associated with poorer overall survival (*Table 4*).

Table 4 Univariate and multivariate Cox regression analyses of the risk factors associated with overall survival

Predictors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age‡	0.99 (0.97–1.01)	0.27	–	–
Female	0.43 (0.16–1.17)	0.10	0.27 (0.09–0.75)	0.01
Body weight‡	1.00 (0.98–1.01)	0.68	–	–
Body mass index‡	0.96 (0.92–1.00)	0.08	–	–
Albumin‡	1.11 (0.74–1.67)	0.6	–	–
Charlson score	0.90 (0.78–1.05)	0.18	–	–
Blood loss‡	1.00 (1.00–1.00)	<0.01	1.00 (1.00–1.00)	<0.001
McKeown	0.82 (0.60–1.12)	0.22	–	–
Minimally invasive surgery	0.71 (0.50–1.01)	0.06	–	–
Non-R0 resection margin	2.91 (2.04–4.15)	<0.01	1.95 (1.30–2.92)	0.001
Late pStage (III + IV)	2.29 (1.68–3.13)	<0.01	1.93 (1.37–2.71)	<0.001
Late pT (III + IV)	2.21 (1.61–3.03)	<0.01	1.53 (1.07–2.19)	0.02
Number of nodes harvested	1.00 (0.98–1.01)	0.53	–	–
Positive pN (I + II + III)	2.00 (1.46–2.75)	<0.01	–	–
Bone mineral density‡	0.97 (0.83–1.13)	0.72	–	–
Subcutaneous adipose tissue area‡†	0.88 (0.75–1.04)	0.15	–	–
Visceral adipose tissue area‡†	0.96 (0.81–1.13)	0.64	–	–
Visceral adipose tissue density‡†	1.06 (0.91–1.24)	0.46	1.16 (0.97–1.36)	0.09
Skeletal muscle area‡†	0.74 (0.88–1.19)	0.74	–	–
Skeletal muscle density‡†	0.93 (0.80–1.09)	0.39	0.85 (0.72–0.996)	0.045

‡, continuous variables; †, hazard ratio corresponds to one standard deviation change in terms of individual variables. HR, hazard ratio; CI, confidence interval.

Discussion

For locally advanced ESCC, nCRT followed by surgery has improved long-term survival. However, pulmonary complications after esophagectomy remain common. Our study underscores that patients with these complications face worse short-term outcomes and overall survival. Importantly, a blend of morphomic and clinical factors emerged as independent predictors of both postoperative pulmonary complications and overall survival in our analysis.

Cigarette smoking, a known risk factor for ESCC, adversely affects pulmonary function (27,28). Similarly, chemoradiotherapy for esophageal cancer often leads to decreased pulmonary function (29). Given that all our patients underwent nCRT for ESCC, it is likely their pulmonary function was compromised. Prior studies consistently link impaired pulmonary function with higher risk of complications (2-4,7). Hence, the relatively high incidence of pulmonary complications (36.2%) observed in our study exceeds rates reported previously (13.6% to 50%) (2-8).

Patients with pulmonary complications had longer stays in the intensive care unit and hospital, as well as higher hospital mortality rates, aligning with previous findings (3,4,8). One study, primarily involving patients with esophageal adenocarcinoma, reported that postoperative pulmonary complications did not affect disease-free survival (10). In contrast, other studies focusing on patients with ESCC demonstrated that postoperative complications, particularly pulmonary complications, were associated with poorer overall survival (11-14). In the current study, we also observed lower 1-, 3-, and 5-year survival probabilities in

ESCC patients with pulmonary complications. The biology, surgical procedures, and therapeutic strategies differ between these two groups, which may explain the differing influence of pulmonary complications on survival.

Postoperative adjuvant therapy has been shown to improve disease-free survival in nonresponsive patients (26). However, those with pulmonary complications may require extended recovery time, potentially delaying the initiation of adjuvant therapy. Thus, these vulnerable patients may face poorer overall survival than those without pulmonary complications. Furthermore, inflammatory processes in patients with pulmonary complications can alter their immune system, potentially affecting cancer biology. These changes may contribute to disease progression and, consequently, negatively impact overall survival outcomes (11-14).

All patients in our cohort underwent either McKeown or Ivor Lewis esophagectomy with one-lung ventilation, a procedure often necessitating higher inspired oxygen fractions to achieve optimal saturation, particularly in patients with compromised pulmonary function. Research by Okahara *et al.* demonstrated that elevated inspired oxygen fractions during one-lung ventilation may increase postoperative pulmonary complications (30). Furthermore, one-lung ventilation can induce bilateral lung injury, with the severity of damage escalating with prolonged occlusion time (31). Previous studies identified longer operation times as a risk factor for postoperative respiratory complications following esophagectomy (9,11,32). In our study, we observed associations between increased intraoperative blood loss, more harvested nodes, and advanced pT staging with postoperative pulmonary complications. These factors likely prolong the duration of one-lung ventilation, thereby contributing to pulmonary complications.

Minimally invasive esophagectomy is increasingly adopted due to its perceived advantages over open esophagectomy in terms of being less invasive. However, the occurrence of postoperative pulmonary complications following minimally invasive esophagectomy remains uncertain (33,34). Yoshida *et al.* reviewed 24,233 esophagectomies from the Japanese National Clinical Database and found that minimally invasive esophagectomy was associated with a lower incidence of postoperative pulmonary complications, especially in patients who had not received neoadjuvant therapy (34). In this cohort study, all patients underwent nCRT. Despite the minimally invasive approach causing less trauma and generally enabling quicker recovery, preoperative radiotherapy can complicate the surgery, prolong operative time, and increase the duration of one-lung ventilation, particularly during minimally invasive esophagectomy. As a result, our study did not find a significant association between the type of surgery and postoperative pulmonary complications.

Adequate lymph node dissection during esophagectomy is crucial for accurate cancer staging and improved survival (35,36). Surgeons often perform lymph node dissection along the recurrent laryngeal nerve to ensure a higher number of harvested nodes, aiming for better staging accuracy. However, thoracoscopic recurrent laryngeal nerve lymph node dissection in patients who have undergone chemoradiotherapy presents challenges despite being considered safe (21). Scholtemeijer *et al.* reported that patients with recurrent laryngeal nerve palsy had a higher incidence of pulmonary complications after esophagectomy (37), consistent with our finding that patients with more harvested nodes experienced increased pulmonary complications.

Advanced pathological staging and inadequate resection margins are well-established predictors of poor overall survival in esophageal cancer (10,15-17). Our study reinforces these findings by demonstrating that non-R0 resection margins, late pStage, and late pT stage are associated with worse overall survival. Moreover, we observed that increased intraoperative blood loss correlates with inferior survival, consistent with similar observations in surgeries for gastric, pancreatic, and colorectal cancers (38-40). Additionally, our results align with Bohanes *et al.*, who reported longer survival among female esophageal cancer patients compared to males (41).

Sarcopenia, characterized by low muscle quantity and quality, has been associated with adverse outcomes (42). A meta-analysis involving 5,965 patients concluded that sarcopenia negatively impacted postoperative pulmonary complications and survival rates (43). Sarcopenia, linked to systemic inflammation, may impair immune function, leading to postoperative complications due to a weakened stress response and poorer survival from an increased risk of residual microscopic disease (11-14,44). However, in these meta-analyses, sarcopenia was predominantly evaluated using the SM index, calculated as the total muscle area divided by height squared, based on the third lumbar vertebra in CT imaging.

In our study, we used analytic morphomics to assess sarcopenia, incorporating not only muscle area but also muscle density. Additionally, instead of limiting the evaluation to the third lumbar vertebra, we analyzed the entire SM profile from CT images. Our findings indicated that sarcopenic patients, particularly those with decreased

SM area rather than SM density, experienced more pulmonary complications after esophageal cancer surgery. Furthermore, patients with lower SM density had poorer overall survival following nCRT and esophagectomy.

In addition to muscle, adipose tissue has also been linked to surgical complications. Li *et al.* demonstrated that a higher VAT area was associated with an increased risk of anastomotic leaks in esophageal cancer surgery (45). Similarly, increased VAT area has been identified as a risk factor for postoperative pulmonary complications following pancreaticoduodenectomy (46). In our study, however, we found that increased VAT density, rather than VAT area, was associated with postoperative pulmonary complications after esophagectomy. This may be attributed to the close relationship between VAT and systemic inflammation (47), which can weaken immune function and increase the risk of postoperative complications (11-14).

There are inherent limitations in this study. Firstly, due to the retrospective design, some pulmonary function test data were missing, limiting the completeness of functional assessment; these data are provided in the supplementary table. Consequently, comprehensive functional parameters, including pulmonary function tests and cardiopulmonary exercise testing, were not incorporated into further analyses. Secondly, being a retrospective cohort, there may be some selection bias. These findings warrant validation in larger, prospective studies.

Conclusions

Novel morphomic variables, combined with traditional clinical factors, are vital in identifying patients at risk for postoperative pulmonary complications and poorer overall survival. This underscores the potential for personalized interventions to mitigate complications and enhance survival outcomes in the future.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1227/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1227/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1227/prf

Funding: This work was supported by Chang Gung Memorial Hospital (CORPG5H0021 and CORPG3J0621).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1227/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201701548B0) on December 26, 2017 and individual consent for this retrospective analysis was waived.

References

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
2. Avendano CE, Flume PA, Silvestri GA, et al. Pulmonary complications after esophagectomy. Ann Thorac Surg 2002;73:922-6.
3. Ferguson MK, Durkin AE. Preoperative prediction of the risk of pulmonary complications after esophagectomy for cancer. J Thorac Cardiovasc Surg 2002;123:661-9.
4. Kinugasa S, Tachibana M, Yoshimura H, et al. Postoperative pulmonary complications are associated with worse short- and long-term outcomes after extended esophagectomy. J Surg Oncol 2004;88:71-7.

5. Law S, Wong KH, Kwok KF, et al. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791-800.
6. Nakamura M, Iwahashi M, Nakamori M, et al. An analysis of the factors contributing to a reduction in the incidence of pulmonary complications following an esophagectomy for esophageal cancer. Langenbecks Arch Surg 2008;393:127-33.
7. Shiozaki A, Fujiwara H, Okamura H, et al. Risk factors for postoperative respiratory complications following esophageal cancer resection. Oncol Lett 2012;3:907-12.
8. Lai G, Guo N, Jiang Y, et al. Duration of one-lung ventilation as a risk factor for postoperative pulmonary complications after McKeown esophagectomy. Tumori 2020;106:47-54.
9. Yu B, Liu Z, Zhang L, et al. Pre- and intra-operative risk factors predict postoperative respiratory failure after minimally invasive oesophagectomy. Eur J Cardiothorac Surg 2024;65:ezae107.
10. D'Annoville T, D'Journo XB, Trousse D, et al. Respiratory complications after oesophagectomy for cancer do not affect disease-free survival. Eur J Cardiothorac Surg 2012;41:e66-73; discussion e73.
11. Baba Y, Yoshida N, Shigaki H, et al. Prognostic Impact of Postoperative Complications in 502 Patients With Surgically Resected Esophageal Squamous Cell Carcinoma: A Retrospective Single-institution Study. Ann Surg 2016;264:305-11.
12. Kataoka K, Takeuchi H, Mizusawa J, et al. Prognostic Impact of Postoperative Morbidity After Esophagectomy for Esophageal Cancer: Exploratory Analysis of JCOG9907. Ann Surg 2017;265:1152-7.
13. Yamashita K, Makino T, Miyata H, et al. Postoperative Infectious Complications are Associated with Adverse Oncologic Outcomes in Esophageal Cancer Patients Undergoing Preoperative Chemotherapy. Ann Surg Oncol 2016;23:2106-14.
14. Saeki H, Tsutsumi S, Tajiri H, et al. Prognostic Significance of Postoperative Complications After Curative Resection for Patients With Esophageal Squamous Cell Carcinoma. Ann Surg 2017;265:527-33.
15. Lagergren J, Smyth E, Cunningham D, et al. Oesophageal cancer. Lancet 2017;390:2383-96.
16. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg 2017;6:119-30.
17. Xie SH, Santoni G, Mälberg K, et al. Prediction Model of Long-term Survival After Esophageal Cancer Surgery. Ann Surg 2021;273:933-9.
18. Sheetz KH, Zhao L, Holcombe SA, et al. Decreased core muscle size is associated with worse patient survival following esophagectomy for cancer. Dis Esophagus 2013;26:716-22.
19. Nishigori T, Okabe H, Tanaka E, et al. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. J Surg Oncol 2016;113:678-84.
20. Chiu CH, Zhang P, Chang AC, et al. Morphomic Factors Associated With Complete Response to Neoadjuvant Therapy in Esophageal Carcinoma. Ann Thorac Surg 2020;109:241-8.
21. Chiu CH, Wen YW, Chao YK. Lymph node dissection along the recurrent laryngeal nerves in patients with oesophageal cancer who had undergone chemoradiotherapy: is it safe? Eur J Cardiothorac Surg 2018;54:657-63.
22. Wang SC, Hsieh CH, Cheng CT, et al. Morphometric Characterisation of an Asian Reference Analytic Morphomics Population (A-RAMP). IRCOBI conference 2019.
23. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. 2022. Available online: https://www.R-project.org/
24. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. Ann Surg 2019;269:291-8.
25. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
26. Hsu HY, Chao YK, Hsieh CH, et al. Postoperative Adjuvant Therapy Improves Survival in Pathologic Nonresponders After Neoadjuvant Chemoradiation for Esophageal Squamous Cell Carcinoma: A Propensity-Matched Analysis. Ann Thorac Surg 2016;102:1687-93.
27. Domper Arnal MJ, Ferrández Arenas Á, Lanas Arbeloa Á. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015;21:7933-43.
28. Sill J. The Effects of Smoking on Pulmonary Function Testing. Chest 2016;149:A591.
29. Gergel TJ, Leichman L, Nava HR, et al. Effect of concurrent radiation therapy and chemotherapy on pulmonary function in patients with esophageal cancer: dose-volume histogram analysis. Cancer J 2002;8:451-60.

30. Okahara S, Shimizu K, Suzuki S, et al. Associations between intraoperative ventilator settings during one-lung ventilation and postoperative pulmonary complications: a prospective observational study. BMC Anesthesiol 2018;18:13.
31. Tekinbas C, Ulusoy H, Yulug E, et al. One-lung ventilation: for how long? J Thorac Cardiovasc Surg 2007;134:405-10.
32. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a Predictor of Postoperative Respiratory Complications in Patients with Esophageal Cancer. Ann Surg Oncol 2015;22:4432-7.
33. Uchihara T, Yoshida N, Baba Y, et al. Risk factors for pulmonary morbidities after minimally invasive esophagectomy for esophageal cancer. Surg Endosc 2018;32:2852-8.
34. Yoshida N, Yamamoto H, Baba H, et al. Can Minimally Invasive Esophagectomy Replace Open Esophagectomy for Esophageal Cancer? Latest Analysis of 24,233 Esophagectomies From the Japanese National Clinical Database. Ann Surg 2020;272:118-24.
35. Rizk N, Venkatraman E, Park B, et al. The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg 2006;132:1374-81.
36. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248:549-56.
37. Scholtemeijer MG, Seesing MFJ, Brenkman HJF, et al. Recurrent laryngeal nerve injury after esophagectomy for esophageal cancer: incidence, management, and impact on short- and long-term outcomes. J Thorac Dis 2017;9:S868-78.
38. Tamagawa H, Aoyama T, Yamamoto N, et al. The Impact of Intraoperative Blood Loss on the Survival of Patients With Stage II/III Pancreatic Cancer. In Vivo 2020;34:1469-74.
39. Shibutani M, Maeda K, Kashiwagi S, et al. The Impact of Intraoperative Blood Loss on the Survival After Laparoscopic Surgery for Colorectal Cancer. Anticancer Res 2021;41:4529-34.
40. Wen ZL, Xiao DC, Zhou X. Does Intraoperative Blood Loss Affect the Short-Term Outcomes and Prognosis of Gastric Cancer Patients After Gastrectomy? A Meta-Analysis. Front Surg 2022;9:924444.
41. Bohanes P, Yang D, Chhibar RS, et al. Influence of sex on the survival of patients with esophageal cancer. J Clin Oncol 2012;30:2265-72.
42. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
43. Fang P, Zhou J, Xiao X, et al. The prognostic value of sarcopenia in oesophageal cancer: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2023;14:3-16.
44. Matsunaga T, Miyata H, Sugimura K, et al. Prognostic Significance of Sarcopenia and Systemic Inflammatory Response in Patients With Esophageal Cancer. Anticancer Res 2019;39:449-58.
45. Li S, Qiu R, Yuan G, et al. Body composition in relation to postoperative anastomotic leakage and overall survival in patients with esophageal cancer. Nutrition 2022;94:111534.
46. Shimizu A, Tani M, Kawai M, et al. Influence of visceral obesity for postoperative pulmonary complications after pancreaticoduodenectomy. J Gastrointest Surg 2011;15:1401-10.
47. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234-41.

Cite this article as: Chiu CH, Zhang P, Lin J, Chang AC, Ross BE, Enchakalody B, Shah NV, Liu YH, Chao YK, Wang SC. Morphomic predictors for post-esophagectomy pulmonary complications and overall survival. J Thorac Dis 2025;17(1):209-219. doi: 10.21037/jtd-24-1227