



Airway interventions for tracheobronchial involvement in esophageal carcinoma: a retrospective cohort outcome study and algorithmic approach

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Background: In advanced esophageal carcinoma (EC), there is limited data on risk factors predicting tracheobronchoesophageal fistula (TEF) formation and survival among patients who required airway interventions.

Methods: A retrospective analysis of consecutive patients with EC, who had airway involvement requiring intervention, was conducted from 1998 to 2018. Demographics, clinical progress, disease stage, treatment and survival outcomes were recorded. Patients were followed up till death or until completion of the study. Survival was estimated with the Kaplan-Meier method and curves compared by log-rank test. Multivariate analyses of risk factors were performed using Cox proportional hazard regression.

Results: A total of 122 patients were included. The median (IQR) survival from time of airway intervention was 3.30 (1.57–6.88) months, while the median (IQR) survival from time of histological diagnosis was 8.90 (4.91–14.45) months. Tumour location within 20 mm of the carina, prior radiotherapy and/or esophageal stenting were significantly associated with formation of TEF. Mid EC [adjusted hazard ratio (HR) 1.9; 95% confidence interval (CI): 1.1–3.2] or presence of TEF (adjusted HR 1.8; 95% CI: 1.0–3.2) were associated with lower survival. Patients receiving chemotherapy (adjusted HR 0.46; 95% CI: 0.25–0.84), or esophageal stenting whether before or after airway intervention (adjusted HR 0.32; 95% CI: 0.15–0.68 and adjusted HR 0.51; 95% CI: 0.29–0.90) were associated with increased survival.

Conclusions: Factors associated with TEF formation include airway location, radiotherapy and prior esophageal stenting, and the development of TEF was associated with poorer survival. An algorithmic approach towards tracheobronchial involvement in EC is proposed based on these findings and a review of the literature.

Keywords: Esophageal carcinoma (EC); airway obstruction; stent; tracheoesophageal fistula (TEF)

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Introduction

Airway involvement may be encountered in esophageal carcinoma (EC) due to proximity of the tracheobronchial tree with the esophagus (1,2). Tracheobronchoesophageal fistulas (TEF) develop in 5–15% of EC patients (2-4), and contribute to increased morbidity and mortality due to recurrent aspiration and pneumonia (5,6). The majority of symptomatic patients present with unresectable advanced disease. As such, management is often centered on palliation of symptoms including dyspnea, pain, and dysphagia, where esophageal stenting has been established as a treatment for dysphagia (3,7-10). Airway interventions including balloon or rigid bronchoscopic barrel dilatation, stenting, thermal photo ablation and tracheostomy have been used in the treatment of airway involvement in EC. However, there is a paucity of literature on airway interventions in EC, with current data originating mostly from small series, which may include primary malignancies other than EC. There is a wide range of survival rates following airway interventions in EC reported in the literature, ranging from 0.8 to 7.1 months (7,11-15). There is also limited data on risk factors for TEF formation and survival in EC patients with airway involvement to guide clinical decision making (6,16,17). This study aims to evaluate risk factors for TEF formation and survival in patients with EC who require airway interventions, and proposes an algorithmic management approach based on the findings and a review of literature. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-138/rc>).

Methods

Electronic medical records were assessed to identify patients diagnosed with EC between 1998 and 2018 at a tertiary medical centre in Singapore. Consecutive patients with EC and also requiring airway intervention for tracheobronchial involvement were included in a retrospective analysis. All patients had bronchoscopic airway evaluation. Patients without bronchoscopic airway evaluation were excluded. Demographics, clinical progress, treatment and survival outcomes were recorded. Staging at the time of diagnosis was determined based on clinical, or pathological staging, if available. A positive change in either patient reported respiratory symptoms such as dyspnea, cough and hemoptysis, or objective measures such as liberation from mechanical ventilation, reduction in oxygen requirements

or improvement in oxygen saturation, were used to define improvement in respiratory symptoms. Patients were followed up till death or until the completion of the study. This study presents additional information on a subset of patients whose data had been previously published (2), analysing data specifically in patients who required airway intervention only. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of SingHealth CIRB C (approval number: 2017-2966). Requirement for informed consent was waived, as the study was retrospective in nature and data was de-identified prior to analysis.

Airway interventions

Airway involvement by EC was diagnosed bronchoscopically and included mucosal invasion (*Figure 1*), extrinsic compression with airway luminal diameter reduced by at least 20% for a length of ≥ 20 mm (*Figure 2*), or TEF (*Figure 3*) (2,18). Malignant tracheobronchial strictures were dilated using controlled radial expansion (CRE) balloons (Microinvasive, Boston Scientific Corporation, Massachusetts, USA) or rigid bronchoscope barrel. Neodymium-doped yttrium aluminium garnet (Nd-YAG) laser (LaserSonic, Milpitas, California, USA) and argon plasma coagulation (Ceralas[®], Biolitec, Jena, Germany) were used for tumour ablation. Tracheostomy was performed for proximal tracheal stenosis. When there was extrinsic compression or luminal obstruction by EC, or presence of TEF, covered self-expanding metallic stents (SEMS) (Ultraflex[™], Boston Scientific Corporation, Massachusetts, USA), or silicone straight or Y-stents (Tracheobronxane[™] Dumon, Novatech, La Ciotat, France) were deployed according to the operator's clinical judgement (*Videos 1,2*) (18).

Anatomical relationship of esophagus to tracheobronchial tree

The upper esophagus [located 15 to 25 centimeters (cm) from upper incisors] comprises of the cervical and thoracic esophagus till the level of the inferior border of the azygos vein. The posterior membranous wall of the trachea is anterior to the esophagus, up to the tracheal bifurcation at the main carina. The mid esophagus (25 to 30 cm from upper incisors) spans the tracheal bifurcation to the proximal left main bronchus, while the lower esophagus (30 to 40 cm from upper incisors) extends from distal left main bronchus to left lower lobe bronchus (19,20).

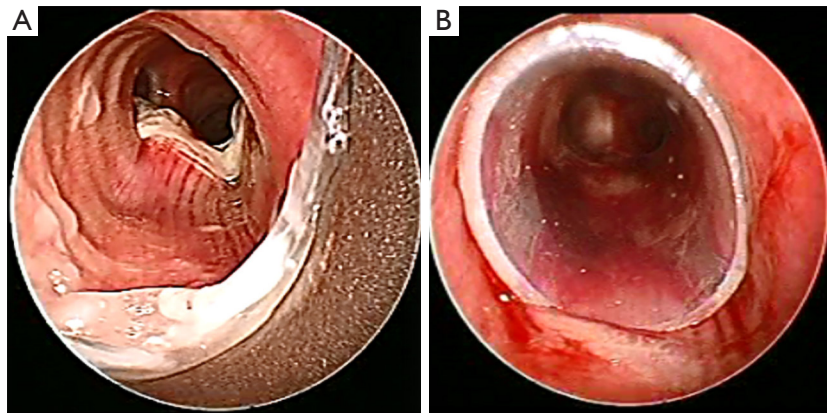


Figure 1 Mucosal tumour invasion seen within 20 mm of carina. (A) Bronchoscopic evaluation revealing tumour invasion of the distal trachea, carina and left main bronchus. (B) The area of mucosal invasion is covered with a silicone Y stent, with the proximal end of Y stent at the mid trachea.

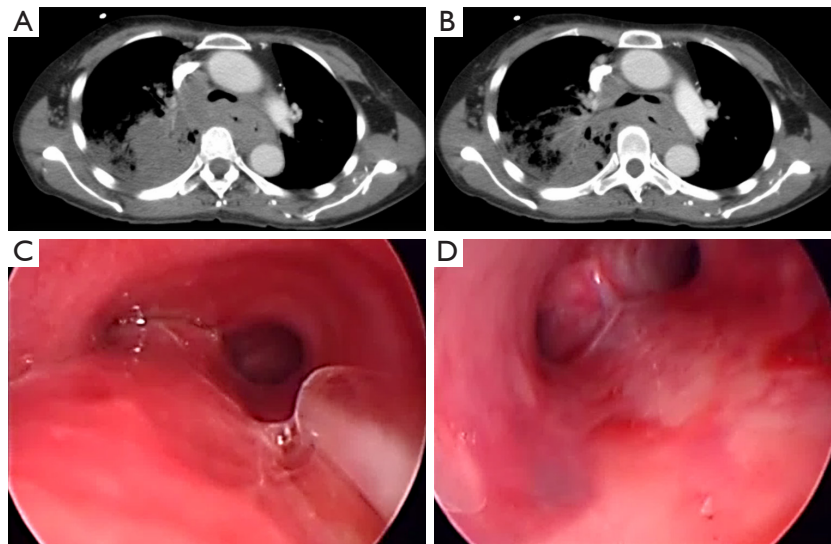


Figure 2 Evaluation and treatment of extrinsic airway obstruction of the carina. (A,B) Computed tomography showing airway obstruction by mid esophageal tumour and adjacent lymphadenopathy causing collapse, as well as consolidation of the right lower lobe. (C) Bronchoscopic evaluation showing complete occlusion of the left main bronchus from the level of the carina. There is no visible tumour invasion of the airway mucosa. (D) Post 15/12/12 mm × 30/30/15 mm (trachea/left main stem bronchus/right main stem bronchus diameter and length) silicone Y-stent deployment with good patency of the airways

Gastroesophageal junction carcinoma rarely causes direct invasion of the tracheobronchial tree because of lack of proximity, and were excluded from analysis.

Statistical analysis

Continuous variables, presented as mean ± standard deviation (SD) or as median (interquartile range, IQR),

were analysed using *t*-tests or Mann-Whitney U tests as appropriate. Discrete variables were analysed using Pearson's chi-square or Fisher's exact test. Cox proportional hazard regression was used to explore associations between survival, patient characteristics, anatomical involvement as well as treatment modalities.

For hazard ratio analysis, survival period was defined as the time from airway intervention to death or till completion

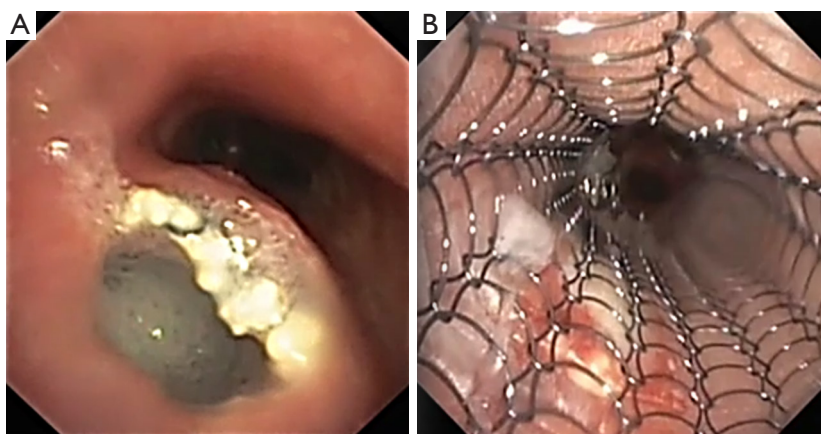
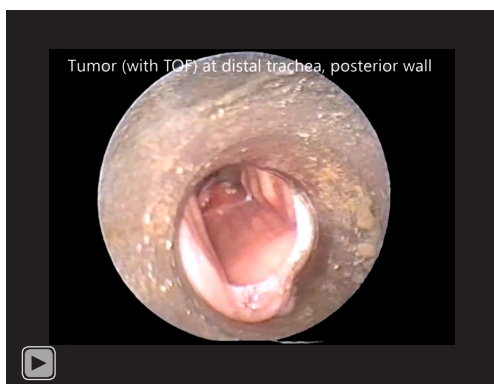
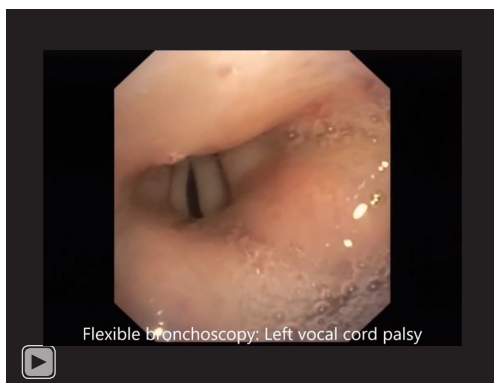


Figure 3 Treatment of a stent associated esophago-respiratory fistula. (A) Bronchoscopic evaluation showing the proximal end of an esophageal stent. There is no evidence of tumour invasion of the airway mucosa. (B) The stent associated esophago-respiratory fistula is covered with a self-expanding metallic airway stent.



Video 1 Esophageal carcinoma with tracheobronchoesophageal fistula and silicone straight stent insertion.



Video 2 Esophageal carcinoma with tracheobronchoesophageal fistula due to esophageal stent, and self-expanding metallic stent insertion.

of study. The Kaplan-Meier method and log-rank test were used to compare the overall survival of patients with and without TEF at time of airway intervention. Statistical differences were considered significant at $P < 0.05$. Statistical analyses were performed using SPSS (SPSS, version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Demographics, airway involvement and treatment (Table 1)

There were 122 patients recruited (Table 1). Squamous cell carcinoma was the histologic subtype in 95.1%. Combined airway mucosal invasion and extrinsic compression (47/122, 38.5%) was the most common bronchoscopic finding followed by TEF (44/122, 36.1%). The left main bronchus was the most common airway site for mid EC ($n=78$), affecting 35/78, 44.9%. Fifty-seven out of 78, 73.1% of mid EC tumours were within 20mm of the carina.

Airway stenting was performed in 100 patients (100/122, 82%). Overall, 15 patients (15/122, 12.3%) underwent tracheostomy to manage airway obstruction. Patients with mid EC required airway stenting in 70/78, 89.7%, compared to lower (8/11, 72.7%) and upper EC lesions (22/33, 66.7%; $p=0.011$). Esophageal stenting was performed in 46/122, 37.7%. Patients with mid EC lesions required esophageal stenting procedures in 38/78, 48.7%, as compared to lower EC (3/11, 27.3%) and upper EC (5/33, 15.1%; $P=0.003$).

Table 1 Patient demographic data, airway involvement and treatment received (n=122)

Characteristics	Number (%)	Upper esophageal carcinoma (n=33), (%)	Mid esophageal carcinoma (n=78), (%)	Lower esophageal carcinoma (n=11), (%)	P value
Patient demographics and airway involvement					
Mean age at diagnosis in years \pm SD	61 \pm 11	59 \pm 12	64 \pm 10	67 \pm 9	0.114
Male gender	109 (89.3)	29 (78.8)	72 (92.3)	8 (72.7)	0.136
Chinese ethnicity	110 (90.2)	29 (78.8)	73 (93.6)	8 (72.7)	0.082
Squamous cell carcinoma	116 (95.1)	32 (97.0)	76 (97.4)	7 (63.6)	<0.001
Stage 3 or 4 at time of diagnosis	98 (80.3)	30 (90.9)	64 (82.1)	4 (36.4)	<0.001
Type of airway involvement					
Mucosal invasion	24 (19.7)	8 (24.2)	13 (16.7)	3 (27.3)	0.526
Extrinsic compression \geq 20%	7 (5.7)	4 (12.1)	3 (3.8)	0 (0)	0.159
Mucosal invasion and extrinsic compression \geq 20%	47 (38.5)	11(33.3)	30 (38.5)	6 (54.5)	0.457
Tracheo-esophageal fistula	44 (36.1)	10 (30.3)	32 (41.0)	2 (18.2)	0.243
Primary site of airway involvement*					
Proximal trachea	23 (18.9)	13 (39.4)	8 (10.3)	2 (18.2)	0.002
Mid trachea	31 (25.4)	14 (42.4)	15 (19.2)	2 (18.2)	0.039
Distal trachea	18 (14.8)	3 (9.1)	15 (19.2)	0 (0.0)	0.136
Carina	3 (2.5)	0 (0.0)	3 (3.8)	0 (0.0)	0.420
Left main bronchus	41 (33.6)	2 (6.1)	35 (44.9)	4 (36.4)	<0.001
Others**	6 (4.9)	1 (3.0)	2 (2.5)	3 (27.2)	0.011
Airway lesions \leq 20 mm from or at the carina	73 (59.8)	10 (30.3)	57 (73.1)	6 (54.5)	<0.001
Airway interventions					
Airway stenting	100 (82.0)	22 (66.7)	70 (89.7)	8 (72.7)	0.011
Tracheostomy	15 (12.3)	10 (30.3)	5 (6.4)	0 (0.0)	<0.001
Treatment received prior to airway intervention					
Radiotherapy	44 (36.1)	13 (4.3)	26 (33.3)	5 (45.5)	0.660
Chemotherapy	52 (42.6)	13 (4.3)	31 (39.7)	8 (72.7)	0.106
Radiotherapy and chemotherapy	33 (27.0)	8 (24.2)	21 (26.9)	4 (36.4)	0.735
Esophageal stenting	17 (13.9)	2 (6.1)	13 (16.7)	2 (18.2)	0.308
Surgery	22 (18.0)	3 (9.1)	13 (16.7)	6 (54.5)	0.003
Treatment received during entire course of disease					
Radiotherapy	96 (78.7)	30 (90.9)	59 (75.6)	7 (63.6)	0.088
Chemotherapy	78 (63.9)	22 (66.7)	48 (61.5)	8 (72.7)	0.715
Radiotherapy and chemotherapy	68 (55.7)	21 (63.6)	41 (52.6)	6 (54.5)	0.560
Esophageal stenting	46 (37.7)	5 (15.1)	38 (48.7)	3 (27.3)	0.003
Surgery	25 (20.5)	6 (18.2)	13 (16.7)	6 (54.5)	0.013

*, data unavailable for 2 patients; **, right main bronchus, left lower lobe, right bronchus intermedius, right middle lobe, left upper lobe, right upper lobe, right lower lobe, apical segment of right lower lobe. SD, standard deviation.

Table 2 Types, complications and outcomes of airway intervention

Airway intervention modalities	n (%) unless specified
Tracheostomy	15 (12.3)
Airway stenting	100 (82.0)
Straight silicone stent	54 (54.0)
Y silicone stent	17 (17.0)
Self-expanding metallic stent	29 (29.0)
Tumour debulking with forceps, laser or argon plasma coagulation	36 (29.5)
Dilatation of stenosis with rigid bronchoscope barrel or balloon dilatation	57 (46.7)
Complications of airway intervention	
Immediate complications	25 (20.5)
Bleeding >50 mLs	5 (20.0)
Failure to deploy stent	9 (36.0)
Trauma*	7 (28.0)
Others**	4 (16.0)
Complications of airway stenting	25 (25.0)
Stenosis of stent from tumour invasion	11 (44.0)
Stent migration	9 (36.0)
Mucus plugging	2 (8.0)
Granuloma formation	3 (11.1)
Stent infection	2 (8.0)
Repeat airway intervention required	29 (23.8)
Airway stenting	13 (44.8)
Ablation with laser or argon plasma coagulation and/or dilatation	16 (55.2)
Stent removal	5 (17.2)
Repeat tracheostomy	3 (10.3)
Outcomes of airway intervention	
Median survival from time of airway intervention in months (IQR)	3.30 (1.57–6.88)
Median survival from time of histological diagnosis in months (IQR)	8.90 (4.91–14.45)
Improvement in respiratory symptoms (n=115)	96 (83.5)
Respiratory-related cause of death (n=97)	64 (66.0)

*, one tracheobronchoesophageal fistula from tracheostomy, one pneumothorax post-airway dilatation, one chipped tooth and four with vocal cord edema attributed to rigid bronchoscope intubation; **, myocardial infarction, dislodged esophageal stent, respiratory failure and mucus plugging requiring intubation. IQR, interquartile range.

Types, complications and outcomes of airway intervention (Table 2)

Straight silicone stents were used in 54/100, 54%, Y silicone stents in 17/100, 17%, and SEMS in 29/100, 29% (Figures 1,3). The proportion of immediate complications

with SEMS was 12/29, 41.4%; compared to silicone stents 10/71, 14.1% (P=0.003). Of those who developed delayed post-stenting complications (25/100, 25.0%); 9/25, 36.0% experienced stent migration. Stent migration involved 6 straight silicone stents, 2 covered SEMS and 1 silicone Y stent.

Table 3 Univariate analysis of characteristics associated with TEF formation

Variables	No TEF (n=78), n (%)	TEF (n=44), n (%)	P value
Mean age at diagnosis in years \pm SD	61 \pm 11	62 \pm 10	0.788
Male gender	70 (89.7)	39 (88.6)	1.000
Stage 3 or 4 at diagnosis	66 (84.6)	32 (72.7)	0.154
Treatment before airway evaluation			
Surgery	12 (15.4)	10 (22.7)	0.311
Chemotherapy	27 (34.6)	23 (52.3)	0.057
Radiotherapy	17 (21.8)	25 (56.8)	<0.001
Chemo- and radiotherapy	13 (16.7)	18 (40.9)	0.003
Esophageal stenting	5 (6.4)	12 (27.3)	0.001
Radiotherapy and esophageal stenting	1 (1.3)	8 (18.2)	0.001
Location of airway lesion			
Airway lesion \leq 20 mm from carina	38 (48.7)	35 (79.5)	0.001
Location of cancer			
Upper esophageal carcinoma	23 (29.5)	10 (22.7)	0.420
Mid esophageal carcinoma	46 (58.9)	32 (72.7)	0.129
Lower esophageal carcinoma	9 (11.5)	2 (4.5)	0.324
Outcomes after airway intervention			
Respiratory-related cause of death	34 (57.6)*	30 (78.9)**	0.031

*, data unavailable for 19 patients; **, data unavailable for 6 patients. TEF, tracheobronchoesophageal fistula; SD, standard deviation.

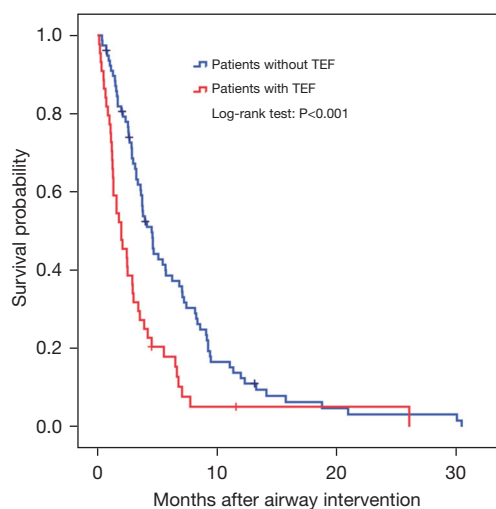


Figure 4 Kaplan-Meier plots of overall survival of patients with and without TEF at time of airway intervention. Median survival from the time of airway intervention was 1.98 (IQR: 0.94–3.02) and 4.52 (IQR: 3.56–5.47) months for patients with TEF and without TEF, respectively ($P<0.001$). TEF, tracheobronchoesophageal fistula.

Patients experienced improvement in respiratory symptoms in 96/115, 83.5% (Table 2). The median (IQR) survival from time of histological diagnosis was 8.90 (4.91–14.45) months, while the median (IQR) survival from time of airway intervention was 3.30 (1.57–6.88) months. Death was attributed to respiratory causes in 66%.

Risk factors for tracheobronchoesophageal fistula formation (Table 3, Figure 4)

On univariate analysis, radiotherapy and/or prior esophageal stenting were significant risk factors for TEF development (Table 3). Among patients with TEFs, airway lesions \leq 20 mm from carina were detected in 35/44, 79.8% as compared to patients without TEF 38/78, 48.7% ($P=0.001$). Patients with TEF died of respiratory-related causes in 78.9%, as compared to 57.6% of those without TEF ($P=0.031$). Median (IQR) survival from the time of airway intervention in patients with TEF was 1.98 (0.94–3.02) months compared to patients without TEF, 4.52

Table 4 Cox proportional hazards regression analysis for determinants of survival after airway intervention

Variables	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at time of intervention	0.983 (0.966–1.000)	0.054	0.993 (0.970–1.016)	0.539
Male gender	1.422 (0.768–2.633)	0.263	1.588 (0.760–3.317)	0.219
Stage 3 or 4 at diagnosis	1.154 (0.713–1.870)	0.560	1.579 (.837–2.980)	0.158
Location of cancer				
Upper esophageal carcinoma	1.000		1.000	
Mid esophageal carcinoma	1.440 (0.940–2.205)	0.094	1.906 (1.133–3.205)	0.015
Lower esophageal carcinoma	0.958 (0.451–2.034)	0.911	0.963 (0.384–2.415)	0.937
Airway involvement \leq 20 mm from carina	1.557 (1.060–2.289)	0.024	1.271 (0.789–2.048)	0.324
Tracheoesophageal fistula	2.050 (1.388–3.028)	0.001	1.832 (1.043–3.216)	0.035
Surgery before airway intervention	1.701 (1.062–2.725)	0.027	0.931 (0.499–1.736)	0.822
Chemotherapy				
No chemotherapy	1.000		1.000	
Chemotherapy before airway intervention	0.939 (0.618–1.427)	0.768	1.234 (0.712–2.138)	0.454
Chemotherapy after airway intervention	0.384 (0.228–0.649)	0.001	0.459 (0.251–0.838)	0.011
Radiotherapy				
No radiotherapy	1.000		1.000	
Radiotherapy before airway intervention	0.937 (0.563–1.560)	0.803	1.053 (0.545–2.032)	0.878
Radiotherapy after airway intervention	0.568 (0.348–0.925)	0.023	0.674 (0.385–1.181)	0.168
Esophageal stenting				
No esophageal stenting	1.000		1.000	
Esophageal stenting before airway intervention	1.015 (0.587–1.758)	0.957	0.316 (0.147–0.679)	0.003
Esophageal stenting after airway intervention	0.852 (0.544–1.335)	0.484	0.511 (0.290–0.902)	0.021
Airway stenting				
No airway stenting	1.000		1.000	
Silicone stent	1.372 (0.820–2.297)	0.229	1.825 (0.961–3.467)	0.066
Self-expanding metallic stent	1.204 (0.669–2.167)	0.537	1.507 (0.746–3.045)	0.253

HR, hazard ratio; CI, confidence interval.

(3.56–5.47) months (*Figure 4*).

Risk factors for survival (Table 4)

On multivariate Cox regression analysis, mid esophageal tumors [adjusted hazard ratio (HR) 1.9; 95% confidence interval (CI): 1.1–3.2] and presence of a TEF (adjusted HR 1.8; 95% CI: 1.0–3.2) were associated with poorer survival (*Table 4*). Chemotherapy after airway intervention (adjusted

HR 0.46; 95% CI: 0.25–0.84), and esophageal stenting either before or after airway intervention (adjusted HR 0.32; 95% CI: 0.15–0.68 and adjusted HR 0.51; 95% CI: 0.29–0.90, respectively) were associated with improved survival.

Discussion

Airway involvement in EC impacts mortality and morbidity (1,2), and there is limited literature from Asia, where the age

standardised rate of EC in males is 20.3 per 100,000, almost 30 times that in Europe and North America (21). Our previously published data showed that airway involvement in EC was associated with poorer survival (2). Among EC patients who needed airway intervention, the present study shows that mid EC and TEF were risk factors for poorer survival, while chemotherapy or esophageal stenting were associated with improved survival. Prior radiotherapy and/or esophageal stenting were associated with TEF development. Fistulas were more commonly found within 20 mm of the carina, reflecting anatomical proximity of the carina to the mid esophagus (3,4,22). This explains why our patients with mid EC were more likely to require airway stenting (70/78, 89.7%) and/or esophageal stenting (38/78, 48.7%), as compared to lower and upper EC. The upper esophagus is adjacent to the proximal trachea, which may not always be amenable to airway stenting if disease is in proximity to the glottis. As such, 10/33, 30.3% of our cases with upper EC were managed with a tracheostomy.

The stent migration rate was 9/100 (9%): 8 involving straight silicone stents or SEMS, and 1 involving silicone Y stent. In 3 cases where straight silicone stents were used, the esophageal tumour had regressed following chemotherapy and/or radiotherapy, which led to stent loosening and ultimately dislodgement. As such, it appears prudent to deploy Y-stents for amenable lesions near the carina. Y-stent limbs straddle the carina and anchor the stent. Covered metallic Y-stents are an alternative to silicone stents if expertise and equipment are available (11,23,24).

Esophageal stenting as well as dual stenting of both the esophagus and airway was associated with improved survival in this study. This observation is despite the association between esophageal stents and TEF formation, suggesting that timing of intervention and sequencing with other treatments may be important. Esophageal intervention relieves dysphagia and can improve quality of life over alternatives such as feeding gastrostomy or jejunostomy (1,3,7,25,26). The European Society of Gastrointestinal Endoscopy recommends esophageal SEMS for malignant TEF, and dual stenting if fistula occlusion is not achieved by either esophageal or airway stenting alone (25). Dual stenting in our study was associated with improved survival, consistent with preceding studies (2,6,12). Dual stenting may be advantageous as it affords a better fistula seal and hence fewer aspiration events, as well as reduced risk of airway obstruction from isolated esophageal stenting.

Stent-associated esophago-respiratory fistulas (SERFs) have been shown to occur following 4% of

esophageal stenting procedures (27). It is hypothesized that the increased radial force exerted on the esophageal mucosa results in ischemic necrosis. This can be further compounded by radiotherapy. Stent-associated esophago-respiratory fistulas occurred more frequently when proximal or mid EC were stented (27). Similarly, ischemic injury from pressure exerted by both esophageal and airway stents during dual stenting present a theoretical risk. However, when dual esophageal and airway stents were used, a case-control study did not find any relationship with SERF development (odds ratio 1.01, 95% CI: 0.054–18.86) (27), lending support to the use of dual stenting.

Seventeen of 46 (37%) patients had esophageal stenting before airway intervention. Tracheal compression following esophageal stenting has been reported in 7–10% (6,13,28). This can cause respiratory distress necessitating emergent esophageal stent removal, especially in the presence of pre-existing tracheal stenosis or extrinsic compression (13). Two such cases were encountered in this study. In addition, 3 out of 9 patients with failed airway stent deployment had undergone prior esophageal stenting. This highlights that emergent airway stenting in EC has the potential for failure. In another study, 5 out of 7 patients admitted for emergency airway stenting following esophageal stent complications had airway stenting failure (15). Therefore, airway stenting should be performed prior to esophageal stenting during sequential dual stenting. This is especially in patients at risk of airway compromise i.e., airway obstruction known to be >50% of airway lumen.

The risk of TEF formation is higher in patients receiving combined esophageal stenting and radiotherapy, which is the reason guidelines do not recommend radiotherapy after esophageal stenting (25,27,29–31). Additionally, randomized controlled trial data show limited improvement in dysphagia or survival with the addition of radiotherapy following esophageal stenting (32). However, data demonstrate the safety of catheter-based brachytherapy when administered after insertion of esophageal SEMS (33,34). This may be considered as an alternative treatment modality.

The present study reflects the largest number of patients with EC requiring airway intervention to date. Limitations include the retrospective nature of the study, which spanned 20 years as treatment of advanced EC continued to evolve. However, the single centre experience and airway interventions performed by a small group of interventional pulmonologists have ensured completeness of data collection and relative standardization of endoscopic technique.

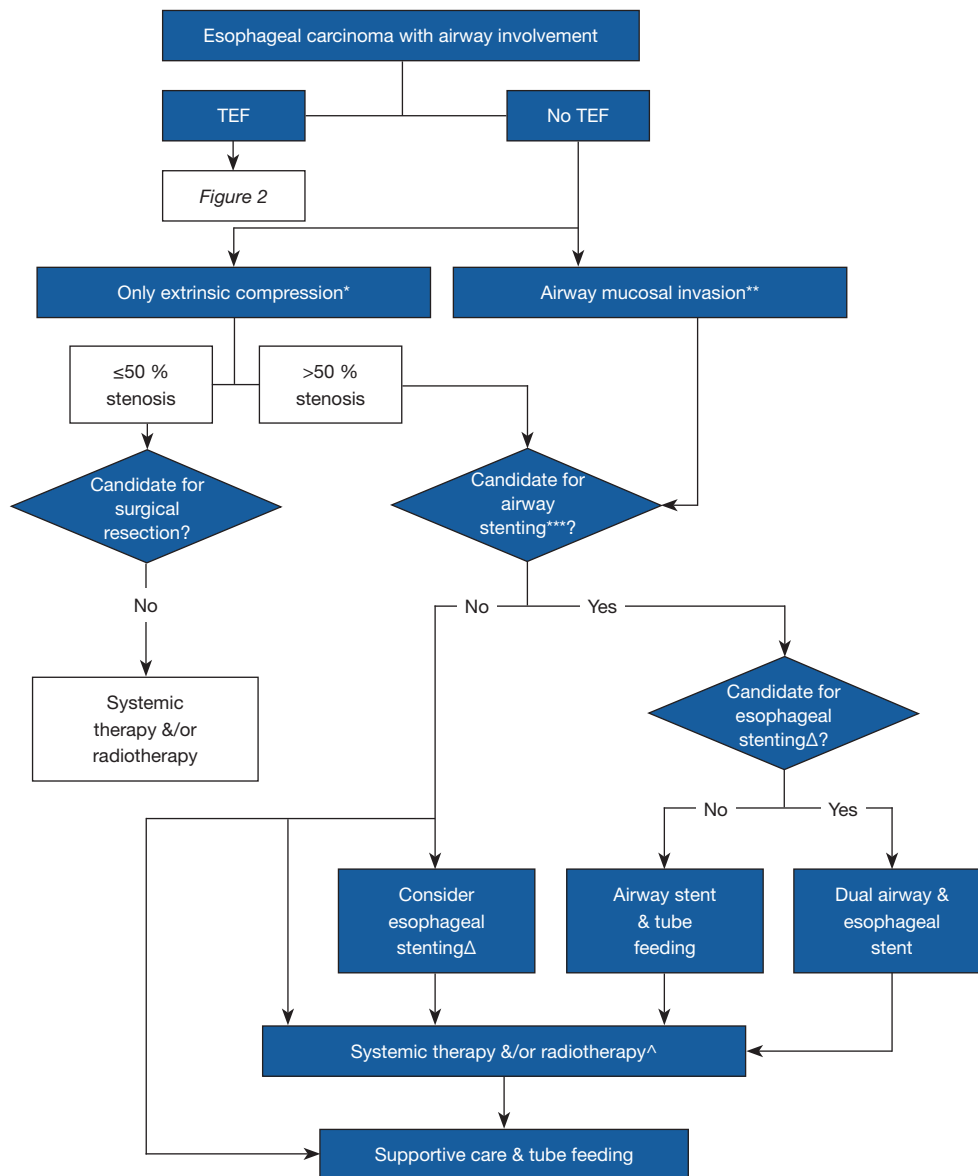


Figure 5 Algorithm for the management of tracheobronchial involvement secondary to esophageal carcinoma. *, we propose close airway surveillance for non-critical ($\leq 50\%$) stenosis, and surgery in appropriate candidates in the absence of mural invasion; **, radial endobronchial ultrasonography may be useful to assess extent of airway wall invasion (35,36); ***, stenting should be considered in the presence of dyspnea; Δ , esophageal stenting should proceed after evaluation of the likelihood of further compromise to airway patency; \wedge , external beam radiotherapy to the esophagus after stenting should be used with caution. Brachytherapy may be an alternative or addition to esophageal stenting for malignant dysphagia (1). TEF, tracheobronchoesophageal fistula.

To date, there is still insufficient data to guide an evidence based approach to airway intervention in advanced EC. To bridge this gap, we summarized the findings from this study, as well as a review of literature into a management algorithm as shown in *Figures 5,6*. First, there should be a low clinical threshold to suspect airway

involvement in patients with EC, and careful bronchoscopic evaluation needs to be undertaken in these patients. This will facilitate early detection of extrinsic compression and mucosal invasion, which should be distinguished from each other. If in doubt, radial endobronchial ultrasonography may be useful to assess extent of airway wall invasion

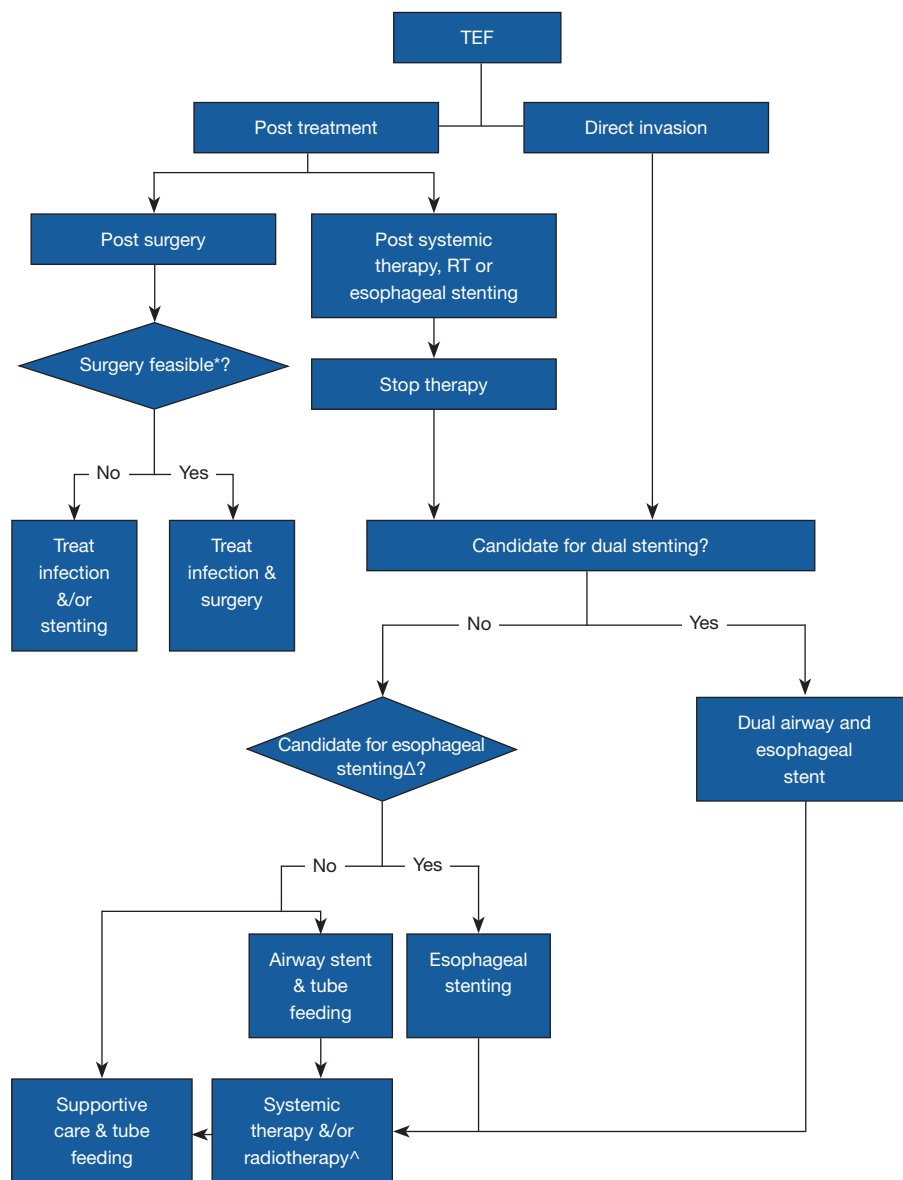


Figure 6 Algorithm for the management of TEF secondary to esophageal carcinoma. *, surgery may considered in patients with appropriate performance status and surgical indication; Δ , esophageal stenting should proceed after evaluation of the likelihood of further compromise to airway patency; \wedge , external beam radiotherapy to the esophagus after stenting should be used with caution. Brachytherapy may be an alternative or addition to esophageal stenting for malignant dysphagia (1). TEF, tracheobronchoesophageal fistula; RT, radiation therapy.

(35,36). Mucosal involvement often results in mixed i.e., extrinsic and intrinsic obstruction, which requires multi-modal therapy. We propose close airway surveillance of non-critical ($\leq 50\%$) extrinsic compression (37), and surgical options may be explored in appropriate candidates in the absence of mural invasion. In cases with significant ($>50\%$) airway stenosis (37), airway and esophageal dual stenting should be considered. In our practice, airway stents should

extend at least 5mm beyond the proximal and distal end of the lesion to ensure adequate coverage. The best fitting stents should be used, as oversized stents risk further fistula extension, stent erosion and compression of adjacent structures. Y stenting is preferred for lesions within 20 mm of the carina to minimise stent migration. Esophageal stenting may proceed if the tumour is deemed unlikely to further compromise airway patency after insertion of the

esophageal stent.

Elective dual airway and esophageal stenting in cases with TEF, and significant tracheobronchial stenosis or mucosal invasion should be considered. Covered SEMs can provide a good TEF seal due to their expandable nature. Airway stents should be placed first during dual stenting to avoid potential airway compromise. Adjunctive systemic therapy including immuno- or chemotherapy may control disease progression post airway intervention (1), and close tracheobronchial surveillance is advisable during the course of oncological therapy. Radiotherapy to the esophagus after stenting should be used with caution. Brachytherapy may be an alternative or used in addition to esophageal stenting for malignant dysphagia (1). Palliation with supportive care, including tube feeding, should also be considered in patients deemed unsuitable for more invasive therapies.

Conclusions

This study represents the largest published cohort of patients with EC and airway involvement to date. The middle esophagus is in close proximity to the airway, and tumours at this location can carry greater morbidity and requirement for airway interventions. Factors associated with TEF formation include location of the tumour in the airways, and prior radiotherapy and/or esophageal stenting. Fistula development was associated with poorer survival. Therefore, careful bronchoscopic evaluation and surveillance is necessary in patients with EC and suspected airway involvement. Y silicone rather than straight stents are preferred for lesions within 20 mm of the carina. Dual stenting affords better fistula seal and should be considered for the management TEF. These findings have been summarised into a proposed treatment algorithm that should be revised as new data emerges.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-138/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-138/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 Institutional Review Board of SingHealth CIRB C (approval number: 2017-2966). Requirement for informed consent was waived, as the study was retrospective in nature and data was de-identified prior to analysis.

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