Airway Ultraflex Stenting in Esophageal Cancer with Esophagorespiratory Fistula

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Abstract: *Introduction:* Esophagorespiratory fistula (ERF) caused by esophageal cancer has a poor prognosis. This study describes the clinical effects of airway ultraflex stenting as an alternative method for ERF caused by esophageal cancer. *Methods:* In an university-affiliated hospital, consecutive patients with ERF caused by esophageal cancer and confirmed by bronchoscopy were included. The demography, clinical manifestations and survival between groups with and without airway stenting were compared by case-control study. *Results:* From 2001 to 2007, 817 patients with esophageal cancer received bronchoscopy. Among these patients, 59 patients with ERF were included in this study. The demography and clinical manifestations between groups with and without airway stenting were similar, but survival improved in group with airway stenting, which was compared using log-rank test [$P = 0.04$; hazard ratio, 0.56; 95% confidence interval (CI), 0.31–0.99]. After adjusted with age and gender by multinominal logistic regression, airway stenting [adjusted odds ratio (OR), 5.2; $P = 0.01$; 95% CI, 1.4–18.8], performance status (adjusted OR, 6.1; $P = 0.004$; 95% CI, 1.8–20.8), further treatment (adjusted OR, 8.7; $P = 0.001$; 95% CI, 2.3–32.8) and prolonged pneumonia (adjusted OR, 0.14; $P = 0.008$; 95% CI, 0.03–0.59) remained as significant factors that impacted survival. *Conclusions:* Surgical treatment remains the first choice in patients with esophageal cancer with ERF; however, the authors provided an alternative airway stenting for those patients whom surgery is unsuitable. It improved survival in the group with airway stenting than those without. Performance status improvement and further treatment for esophageal cancer may improve survival, but prolonged pneumonia may worsen survival.

Key Indexing Terms: Airway Ultraflex stents; Esophageal cancer; Esophagorespiratory fistula; Outcomes. **[Am J Med Sci 2012;344 (2):105–109.]**

Advanced unresectable esophageal cancer with airway invasion has a very poor prognosis. Patients with this condition face not only limited life expectancy but also many potentially debilitating complications.[1–3] For tumors extending into the airway lumen, the primary goals of therapy are for the palliative relief of the malignant obstruction of the esophageal lumen and central airway and to close the fistula between the esophagus and central airway. Palliative options include mechanical core-out, dilatation, laser ablation, electrocautery, cryotherapy, photodynamic therapy and brachytherapy.[4] However, satisfactory results may not be immediate or lasting. Among the conditions with airway involvement by esophageal cancer, esophagorespiratory fistula (ERF) causes the worst prognosis.[1–4]

In the past decade, endoscopic stenting has gained acceptance as the preferred palliative therapy for airway complications in unresectable esophageal cancer.[5] Stenting is effective for airway stenosis from both extrinsic compression and direct tumor invasion and has also been shown to be useful in the treatment of ERF.[6–8] Among patients with obstruction of the trachea and main stem bronchi with tumor invasion, respiratory failure is one of the most severe complications. Because of advances in airway stents and insertion techniques, interventional bronchoscopic procedures have been reported to facilitate weaning from mechanical ventilation.[9,10] Moreover, covered self-expandable metallic stents (SEMS) have been used to seal off tracheo-esophageal fistulas and to avoid aspiration symptoms.[6,11–12] For difficulty of ERF management, limited studies reported the effect of airway metallic stent placement in ERF caused by esophageal cancer.

The most common methods of stent placed in patients are rigid bronchoscopy under general anesthesia and flexible bronchoscopy under fluoroscopic guidance. However, some patients are not suitable for surgical intervention or rigid bronchoscopy with a general anesthetic because of the severity of their illness and comorbidities or their refusal to have surgery. In addition, fluoroscopy requires special facilities that may not be available in every institution.

We designed this study at Chang Gung Memorial Hospital, a university-affiliated hospital in Taiwan. We collected data with and without airway Ultraflex stent placement among those patients with esophageal cancer who had ERF. To compare demography, clinical manifestations and survival between the groups with and without SEMS and to find out possible independent factors that impact survival of these subjects, we conducted this study to clarify the role of metallic stents in patients with ERF caused by esophageal cancer.

PATIENTS AND METHODS

Design

This investigation was a retrospective case-control study. Informed consent was obtained from all patients or their representatives before stent implantation. The methodology, assurance of patient confidentiality and design of the project were all approved by our institutional review board (IRB no. 99-0337B).

Patients

From August 2001 to March 2007, consecutive patients with esophageal cancer received bronchoscopy for routine airway evaluation when esophageal cancer was diagnosed. Among these subjects, patients with ERF found during

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bronchoscopy and confirmed by esophagograhy were included in this study. Because of illness severity, high surgical risk or surgical refusal, none of these patients were candidates for surgery or stent implantation under rigid bronchoscopy.

Definition of Clinical Manifestations of ERF

Clinical manifestations were according to chart record. Including new development of dyspnea, chronic cough more than 8 weeks, hemoptysis and even respiratory failure. For underlying esophageal cancer, bronchoscopy was routinely arranged after excluding other causes such as anemia, congestive heart failure, airway disease exacerbation, etc.

Decision of Airway SEMS Placement or Not

In our hospital, most patients with esophageal cancer with ERF were referred by medical oncologists. However, there was no standard of SEMS insertion in ERF in esophageal cancer during the study period. It means that not all oncologists referred the patients for SEMS insertion! In this study, all patients with ERF referred by oncologists were suggested SEMS placement, except those patients who refused surgery. All patients in this study were included according to medical records, retrospectively.

Stent Implantation

All patients in our study received a covered Ultraflex (Boston Scientific, Natick, MA) SEMS composed entirely of a single strand of nickel-titanium alloy. The choice of stent length was determined by a previous endoscopic examination, chest x-ray and chest computed tomography scan. The principles of SEMS placement and assessment of stent condition through flexible bronchoscopy under sedation and local anesthesia in our institution have been well reported in previous studies.[13–16] Briefly, sedation with intravenous midazolam (before 2006), or propofol under bispectral index for consciousness monitor (after 2006) and a local anesthesia with 2% xylocaine solution was performed during bronchoscopy. The saturation of oxygen, blood pressure and electrocardiography were monitored during bronchoscopy. The bronchoscope was advanced through a mouth guard into tracheal or bronchial lumen. The bronchoscope was inserted at the proximal end of the lesion. A guide wire was inserted through the bronchoscope and passed through the airway lesion and then the bronchoscope was withdrawn, leaving the guide wire at the lesion site. The bronchoscope was then reinserted into the airway to confirm the location of the guide wire. Under bronchoscopic visualization, the delivery catheter (Boston Scientific) was advanced over the guide wire to deploy the stent. The delivery catheter, guide wire and bronchoscope were then withdrawn, leaving the stent in the lesion site. After completing stent deployment, the bronchoscope was introduced to check the position of the stent.

Assessment of Factors That Impact 90-Day Mortality After ERF Diagnosis or Management

Factors that impacted 90-day mortality were evaluated. These factors included performance status improvement (after SEMS placement or when ERF diagnosed in those patients without SEMS placement), previous treatment when ERF diagnosis, stage IV of esophageal cancer when ERF diagnosis, ERF location and prolonged pneumonia (whether with or without SEMS placement).

Statistical Analysis

All data were expressed as median values and the interquartile range (IQR) or numeric values (%). Because most continuous variables were skewed, nonparametric approaches are used in the study. Quantitative variables between 2 groups were compared using the Mann-Whitney U test for continuous variables and the χ^2 test for nominal variables. The factors that impacted 90-day mortality were entered into a multinominal logistic regression analysis to identify the net effects of each individual factor. The 90-day mortality was the single-dependent variable. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were computed by logistic regression model analysis to clarify the impact of several potentially independent factors by controlling for age and gender. The level of statistical significance was set at $P < 0.05$. Survival days and rate were compared with 2 subgroups with or without SEMS placement. Survival curves were traced using the Kaplan-Meier method, and survival curves were compared using the log-rank test. All analyses were conducted using SPSS software (version 10.0, SPSS, Chicago, IL) and Prism 4 for Windows (version 4.03, Graphpad Software Inc., San Diego, CA).

RESULTS

From August 2001 to March 2007, 817 consecutive patients with esophageal cancer received bronchoscopy for routine airway evaluation when esophageal cancer was diagnosed. Fifty-nine patients with ERF found during bronchoscopy and confirmed by esophagograhy were included in this study. The demography of these subjects with (n = 31) and without (n = 28) airway SEMS placement was listed in Table 1. The demography including age [median (IQR), 56 years (44–66 years) versus 52 years (48-57 years); $P = 0.82$], gender (male, 30 versus 28; $P = 0.34$), performance status (number of patients with performance status less than 2, 5 versus 5; $P = 0.86$), site of fistula (trachea, 15 versus 14; $P = 0.9$; main carina, 0 versus 2; $P = 0.13$; left main bronchus, 10 versus 9; $P = 0.99$; right main bronchus, 6 versus 3; $P = 0.36$), staging (stage III, 22 versus 19; $P = 0.8$) and previous treatment [no treatment, 7 versus 5; $P = 0.65$; concurrent chemoradiotherapy (CCRT), 18 versus 12; $P = 0.24$; chemotherapy, 3 versus 4; $P = 0.58$; CCRT and surgery, 2 versus 5; $P = 0.18$; CCRT, surgery and chemotherapy, 1 versus 2; $P = 0.49$] of esophageal cancer when ERF diagnosed was similar in both groups (Table 1).

Clinical manifestations of these patients with and without SEMS placement was listed in Table 2. The manifestations between patients with and without SEMS including dyspnea [n, 12 (38.7%) versus 9 (32.1%); $P = 0.6$], chronic cough [n, 11 (35.5%) versus 14 (50%); $P = 0.26$], hemoptysis [n, 3 (9.7%) versus 2 (7.1%); $P = 0.73$] and respiratory failure [n, 5 (16.1%) versus 3 (10.8%); $P = 0.54$] were without significant differences.

The median survival period of the 59 patients from the first time of ERF diagnosed was 30 days (IQR, 15–103 days). In patients with an implanted SEMS, the median survival period was 69 days (IQR, 16–120 days), and in patients who were treated without SEMS, it was 21 days (IQR, 6–73 days). The differences between the groups with and without SEMS implanted were significant. The proportion of patients surviving with and without SEMS were traced after ERF diagnosed with the Kaplan-Meier method (31% versus 25%; log-rank test, $P = 0.04$; hazard ratio, 0.56; 95% CI, 0.31–0.99) in Figure 1.

The variables including performance status improvement, received further treatment after ERF diagnosis, previous treatment when ERF diagnosis, stage IV of esophageal cancer when ERF diagnosis, ERF location, prolonged pneumonia and 90-day survival were analyzed with Fisher's test (Table 3).

TABLE 1. Demography of patients with esophageal cancer with ERF on diagnosis

Characteristics	All	With stent	Without stent	*P*
Patient numbers	59	31	28	
Age, median (IQR) (yr)	53 (46–62)	56 (44–66)	52 (48–57)	0.82
Gender, male	58	30	28	0.34
Performance status				0.86
<2	10	5	5	
>2 or =2	49	26	23	
Site of fistula				
Trachea	19	15	14	0.9
Main carina	2	0	2	0.13
Left main bronchus	19	10	9	0.99
Right main bronchus	9	6	3	0.36
Stage				0.8
III	41	22	19	
IV	18	9	9	
Previous treatment				
Nil	12	7	5	0.65
CCRT	30	18	12	0.24
Chemotherapy	7	3	4	0.58
CCRT and surgery	7	2	5	0.18
CCRT, surgery and chemotherapy	3	1	2	0.49

ERF, esophagorespiratory fistula; IQR, interquartile range; CCRT, concurrent chemoradiotherapy.

Performance status improvement, received further treatment after ERF diagnosis and prolonged pneumonia with significant differences between case and control were further analyzed by multiple logistic regression analysis controlling for age and gender. The results are presented in Table 3. Performance status improvement (adjusted OR, 6.1; $P = 0.004$; 95% CI, 1.8–20.8), received further treatment after ERF diagnosis (adjusted OR, 8.7; $P = 0.001$; 95% CI, 2.3–32.8) and prolonged pneumonia (adjusted OR, 0.14; $P = 0.008$; 95% CI, 0.03–0.59) remained significant factors that impact 90-day mortality after controlling for other variables. Previous treatment when ERF diagnosed, stage of esophageal cancer when ERF diagnosed and ERF location failed to maintain their impacted value for the 90-day mortality in the adjusted analysis (Table 3).

TABLE 2. Clinical manifestations of ERF

Manifestations	With stent	Without stent	*P*
Total numbers	31	28	—
Dyspnea, n (%)	12 (38.7)	9 (32.1)	0.6
Chronic cough	11 (35.5)	14 (50)	0.26
Hemoptysis	3 (9.7)	2 (7.1)	0.73
Respiratory failure	5 (16.1)	3 (10.8)	0.54

ERF, esophagorespiratory fistula.

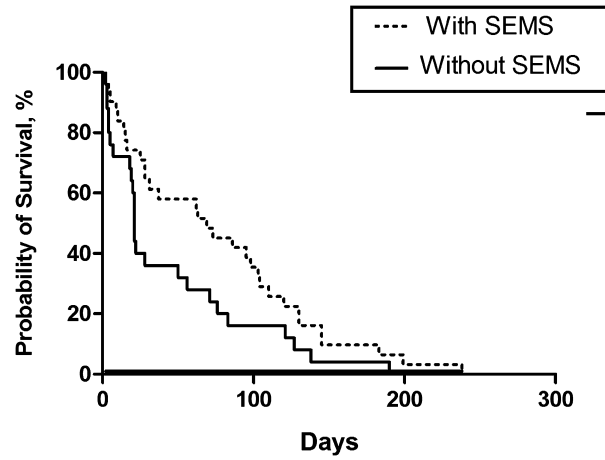

FIGURE 1. The proportion of patients surviving with and without self-expandable metallic stent (SEMS) were traced after esophagorespiratory fistula (ERF) was diagnosed with the Kaplan-Meier method (31% versus 25%; log-rank test, $P = 0.04$; hazard ratio, 0.56; 95% confidence interval, 0.31–0.99).

DISCUSSION

Previous studies have shown that patients with direct airway invasion by esophageal cancer have a poor prognosis.[1–3] However, there are a few reports[9,10] that describe the airway stents in patients with ERF caused by esophageal cancer. Despite their poor prognosis, we have shown in this study that airway Ultraflex stent placement in these subjects is feasible with a flexible bronchoscope.

We report here 59 attempts of esophageal cancer involving the airway in patients with ERF. Bronchoscopic airway stenting without fluoroscopic guidance was successfully performed in 31 patients and no patients failed stenting. Those with SEMS placement had better survival than those without airway SEMS placement, and the possible reasons included improved performance status and received further treatment after SEMS placement. However, conducting this study, we emphasized the potential value of a therapeutic airway stenting for these advanced esophageal cancer. Although airway stent's usefulness has been published a decade ago in those with advanced end-stage esophageal cancer with airway involvement, ERF is still a challenging condition for physicians. There are no current guidelines for airway stent procedures advising for flexible bronchoscopy before stent insertion. Recurrent aspiration pneumonia may be induced during airway invasion by esophageal cancer in these patients with ERF, which therefore suggests poor prognosis. However, we think the effects of the airway stenting by fiber-optic bronchoscopy such as in our study subjects are so positive that considering stenting should be mandatory to improve the possibilities for patients' outcomes.

This alternative method of airway Ultraflex stenting, using flexible bronchoscopy without fluoroscopic guidance, was successful in all patients in our study. The mean time required for stent placement was 16.7 minutes (range, 11.6–27.9 minutes). Despite there were appropriate factors to impact survival after airway stenting in our study, prolonged pneumonia remained to worsen survival even in successful airway stenting. However, no life-threatening complications developed as a result of this procedure. The use of the present technique also provides broader accessibility for patients unsuitable for surgery and would be a viable alternative when surgical or fluoroscopic equipment is not available. The most important is

TABLE 3. Adjusted odds ratio[a] for factors that impact 90-day mortality of patients with esophageal cancer after ERF diagnosis

	Univariate analysis			Multivariate analysis		
Factors	Case (with SEMS placement, n = 31)	Control (without SEMS placement, n = 28)	*P*	Adjusted odds ratio[a]	*P*	95% Confidence interval
Performance status improvement[b]	21 (67.7)	0 (0)	<0.0001	6.1	0.004	1.8–20.8
Received further treatment after ERF diagnosis[b]	13 (41.9)	1 (3.6)	0.0005	8.7	0.001	2.3–32.8
Previous treatment when ERF diagnosed	24 (77.4)	23 (82.1)	0.5	—	—	—
Stage IV esophageal cancer when ERF diagnosed	9 (29.0)	9 (32.1)	0.8	—	—	—
ERF location	15 (48.4)	14 (50.0)	0.9	—	—	—
Prolonged pneumonia[b]	18 (58.1)	27 (96.4)	0.0005	0.14	0.008	0.03–0.59
90-day mortality	13 (41.9)	4 (14.3)	0.02	—	—	—

Values are expressed as n (%) or range.
[a] Adjusted by age and gender in multinominal logistic regression analysis.
[b] *P* value for difference between groups <0.05.
ERF, esophagorespiratory fistula; SEMS, self-expandable metallic stent.

that the patients had better survival when their performance status improved and they could receive further management such as chemotherapy.

The use of silicone stents versus SEMS, stent placement by fiber-optic bronchoscopy versus rigid bronchoscopy, airway versus esophageal stents or whether to use double stenting in both the esophagus and airway remain controversial, however.[7,17] Rigid bronchoscopy under general anesthesia and flexible bronchoscopy under fluoroscopic guidance are the most common methods of stent implantation in mechanically ventilated patients. Despite this, some patients are not suitable for this kind of surgical intervention because of the severity of their illness, comorbidities or a simple refusal to undergo surgery. In addition, fluoroscopy requires special facilities that may not be available in every intensive care unit. However, esophageal stent was used to improve swallowing due to esophageal obstruction. Few stents placed in esophageal cancer for respiratory symptoms, except those difficult to approach by airway stents such as ERF were located at main carina.

There were 2 patients with carina ERF receiving airway stents in current study. However, incomplete closure and leakage were found in the 2 patients. Y stent is suggested for carina ERF. Usually, the patients were referred to surgeon for surgical treatment. However, the 2 patients in our current study refused general anesthesia and surgery. Carinal ERF was found in patients with benign diseases such as traumatic injury in our hospital. Surgical treatment such as repair or Y-stent insertion is the first choice in our hospital. The current study included patients before 2007 and therefore metallic Y stent had not yet been available at our hospital at that time. However, management of carina ERF due to esophageal cancer remains challenging. The life quality and survival are difficult to improve under current treatment. The treatment is also limited by facilities and techniques are available.

Paganin et al.[17] reported double stents (both airway and esophageal) insertion in ERF may increase the efficiency of ERF closure in 2008. However, all included patients in our study were before 2007 and experienced respiratory symptoms (Table 2), which caused airway SEMS indicated. Esophageal stent in our hospital is indicated in gastrointestinal tract symptoms/signs due to esophageal obstruction. However, esophageal stents may cause respiratory symptoms with airway compression. Also, these patients with ERF had advanced stage cancer. Therefore, they usually had received nasoduodenal tube or jejunostomy feeding in our hospital. However, there was limited experience with esophageal stent or double stent insertion in esophageal cancer with ERF in our hospital before 2007. The current data could not conclude the effect of esophageal stent or double stent insertion, but we agreed Paganin's opinion by their report.[17]

Our study has limitations. First, we did not perform a prospective controlled study for airway stents. However, we did not find any obvious diversity signifying that airway stenting did not worsen the survival. Blinded, randomized and controlled trials are hard to perform in these subjects due to the practices. Second, quality of life of these patients was not recorded but only performance status. However, SEMS placement improved most respiratory symptoms and signs in this study; hence, further treatment was possible. There may be bias among 28 patients without SEMS placement for the retrospective character such as it is possible that these 28 patients were not properly evaluated; the ERF may be therefore misdiagnosed or underdiagnosed. Meanwhile, care of these patients also depends on facilities, physicians experience and skills. However, the demography between patients with and without SEMS has been well compared in Table 1. The age, gender, performance status, stage, sites of ERF and previous treatment were not significantly different between the groups! We emphasized that the conditions between the 2 groups were similar. Finally, factors that impacted survival may be complex to analyze, despite our study revealed the better outcome by SEMS placement.

In conclusion, the current study described that airway stenting in ERF patients caused by esophageal cancer improved survival than those without stenting. Surgical treatment remains the first choice in these patients; however, we provided an alternative management for the patients whom surgery is unsuitable. Performance status improvement after stenting and further treatment for esophageal cancer may improve survival and prolonged pneumonia may worsen survival.

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