Comparison of clinical features and stent placement outcomes between airway stenosis caused by primary pulmonary malignancies and that caused by primary non-pulmonary malignancies

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Abstract

Background: Primary pulmonary malignancies (PPMs) and non-pulmonary malignancies (PNPMs) may result in airway stenosis requiring stenting. This study aimed to compare and evaluate the clinical features and stent placement outcomes of airway stenosis caused by PPMs and PNPMs.

Methods: A total of 141 patients with malignant airway stenosis who underwent Micro-Tech stent placements between January 2004 and October 2017 at Department of Respiratory Medicine, Beijing Tian Tan Hospital, Capital Medical University were divided into PPM ($n=100$) and PNPM groups ($n=41$). Patients' clinical features and stent placement outcomes were collected and analyzed. Chi-square test was used to compare the categorical variables, while independent- or paired-sample t test was used to compare the continuous variables.

Results: There were no significant differences in age, sex, treatment history, respiratory symptoms, and incidence of obstructive pneumonia between groups. Multiple airway involvement (63.0% *vs.* 31.7%; $\chi^2=11.459$, $P=0.001$) and atelectasis (17.0% *vs.* 2.4%; $\chi^2=5.536$, $P=0.019$) were more common in the PPM group, while extraluminal obstruction (24.4% *vs.* 6.0%; $\chi^2=8.033$, $P=0.005$) was more common in the PNPM group. Before stenting, the American Thoracic Society Dyspnea Index (ADI) and Karnofsky Performance Scale (KPS) scores showed no significant differences between groups (all $P>0.05$). After stenting, a satisfactory rate of symptom improvement was achieved in both groups (98.0% and 100.0% in the PPM and PNPM groups, respectively; $\chi^2=0.016$, $P=0.898$); ADI and KPS scores, which showed no significant differences between groups (all $P>0.05$), were significantly improved in each group (all $P<0.001$). Complications after stenting could be effectively managed using bronchoscopic procedures.

Conclusions: Among cases of malignant airway stenosis requiring stenting, those caused by PPM are more likely to involve multiple airways and are associated with atelectasis, while those caused by PNPM are more likely to cause extraluminal obstruction. Micro-Tech stent placement has the same immediate effect in terms of improvement in respiratory symptoms and performance status for both malignant airway stenosis caused by PPM and that caused by PNPM.

Keywords: Airway obstruction; Malignancy; Self expandable metal stents; Bronchoscopy

Introduction

Malignant central airway obstruction (CAO) is an intractable disease and is often life-threatening. Various malignant tumors, including primary pulmonary malignancies (PPMs) and non-pulmonary malignancies (PNPMs), can involve the airway, leading to CAO.[1] Resection, if possible, is the preferred therapy for patients with this disease. However, when diagnosed at an advanced stage, most patients lose the chance of surgery and, therefore, require multimodality palliation.[2] Stent placement is usually performed in patients who have exhausted all other treatment modalities or as a transitional treatment to relieve life-threatening airway obstruction. A variety of airway stents made of different materials have been developed. Self-expandable metallic stent is one of the widely used airway stents in patients with malignant airway stenosis. At present, there is still a lack of relevant literature on the comparison of clinical features and stent placement outcomes between malignant airway stenosis caused by PPM and that caused by PNPM. In this study, we reported a 14-year experience with stent placement for malignant CAO. Clinical data obtained from patients who underwent airway stent placement due to malignant CAO from January 2004 to October 2017 in Beijing Tian Tan

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Hospital, Capital Medical University were retrospectively reviewed. The clinical features and stent placement outcomes of malignant CAO caused by PPM and PNPM were compared and analyzed.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Beijing Tian Tan Hospital, Capital Medical University. All patients agreed and signed informed consent forms before stent placement.

Patients

In the 14-year period, a total of 141 patients (104 men) with a median age of 60 years (range, 23–83 years) were enrolled in this study. Data including demographics, etiologies, symptoms, treatment histories, locations and classification of the obstruction, and outcomes after stent placement were collected. The etiologies of malignant airway stenosis were determined by pathological findings in our hospital or by clear medical histories. The classification of malignant airway stenosis was divided into endoluminal, extraluminal, and mixed obstruction.[3] The locations and classification of the central airway lesions were assessed by bronchoscopy combined with thoracic computed tomography (CT). The stents used in this study were all self-expandable metallic stents (Micro-Tech, Nanjing, China), including straight and bifurcated shapes, which were placed by experienced interventional pulmonologists in our hospital. The efficacy of stent placement was assessed according to symptomatic improvement and changes in the Karnofsky Performance Scale (KPS) scores and the American Thoracic Society Dyspnea Index (ADI) before and after stent placement.[4]

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD). Statistical analysis of the data was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Independent-sample *t* test was used to compare ADI and KPS scores between groups, and paired-sample *t* test was used to compare the changes in ADI and KPS scores before and after stenting. Pearson or continuity-corrected chi-square test was used to compare the categorical variables. A value of $P < 0.05$ was defined as statistically significant.

Results

Clinical features

Of all the 141 patients with malignant CAO requiring stent placement, 70.9% (100/141) had PPM and 29.1% (41/141) had PNPM; 58.9% (83/141) had a treatment history including surgery (26.2%, 37/141), chemotherapy (31.2%, 44/141), radiotherapy (24.8%, 35/141), and bronchoscopic intervention (15.6%, 22/141). Before stent placement, chest CT findings showed that 12.8% (18/141) of patients had atelectasis and 18.4% (26/141) had obstructive pneumonia.

Table 1: Etiology of all 141 patients with malignant airway stenosis.

Etiology	*n*	% within group	% in all 141 patients
PPM group ($n=100$)			
Squamous cell carcinoma	55	55.0	39.0
Adenocarcinoma	17	17.0	12.1
Adenoid cystic carcinoma	15	15.0	10.6
Small cell carcinoma	7	7.0	5.0
Undifferentiated carcinoma	3	3.0	2.1
Mucoepidermoid carcinoma	2	2.0	1.4
Large cell carcinoma	1	1.0	0.7
PNPM group ($n=41$)			
Esophageal cancer	26	63.4	18.4
Thyroid cancer	6	14.6	4.3
Malignant lymphoma	4	9.8	2.8
Liver cancer	2	4.9	1.4
Renal cell carcinoma	1	2.4	0.7
Thymoma	1	2.4	0.7
Malignant melanoma	1	2.4	0.7

PPM: Primary pulmonary malignancy; PNPM: Primary non-pulmonary malignancy.

The main respiratory symptoms included dyspnea (93.6%, 132/141), cough (80.1%, 113/141), blood-stained sputum (41.1%, 58/141), hoarseness (9.2%, 13/141), and stridor (4.3%, 6/141). According to the etiologies of the diseases, the 141 patients were divided into PPM ($n=100$) group and PNPM ($n=41$) group [Table 1].

The clinical features between the 2 groups are shown in Table 2. There were no significant differences in age (59.2 ± 11.3 years *vs.* 61.3 ± 11.7 years; $t=-0.918$, $P=0.360$), sex (male, 74.0% *vs.* 73.2%; $\chi^2=0.010$, $P=0.919$), treatment history (57.0% *vs.* 63.4%; $\chi^2=0.494$, $P=0.482$) including surgery (22.0% *vs.* 36.6%; $\chi^2=3.196$, $P=0.074$), chemotherapy (32.0% *vs.* 29.3%; $\chi^2=0.101$, $P=0.751$), radiotherapy (24.0% *vs.* 26.8%; $\chi^2=0.125$, $P=0.724$) and bronchoscopic intervention (15.0% *vs.* 17.0%; $\chi^2=0.125$, $P=0.724$), and respiratory symptoms including dyspnea (93.0% *vs.* 95.4%; $\chi^2=0.008$, $P=0.929$), cough (82.0% *vs.* 75.6%; $\chi^2=0.746$, $P=0.388$), blood-stained sputum (42.0% *vs.* 39.0%; $\chi^2=0.106$, $P=0.744$), hoarseness (11.0% *vs.* 4.9%; $\chi^2=0.673$, $P=0.412$), and stridor (2.0% *vs.* 9.8%; $\chi^2=2.601$, $P=0.107$), and obstructive pneumonia (18.0% *vs.* 19.5%; $\chi^2=0.044$, $P=0.833$) between the 2 groups. The airway lesions involving multiple central airways (63.0% *vs.* 31.7%; $\chi^2=11.459$, $P=0.001$) and atelectasis (17.0% *vs.* 2.4%; $\chi^2=5.536$, $P=0.019$) were more common in the PPM group, while extraluminal obstruction (24.4% *vs.* 6.0%; $\chi^2=8.033$, $P=0.005$) was more common in the PNPM group.

Stent placement outcomes

A total of 145 bare stents (straight, 117; Y-shaped, 28) were successfully inserted in all patients without severe procedure-related complications. There was no significant difference in the proportion of Y-shaped stents used in the 2 groups (22.1%, 23/104 *vs.* 12.2%, 5/41; $\chi^2=1.857$, $P=0.173$). After stent placement, satisfactory immediate

Table 2: Clinical features of 100 patients with PPM and 41 patients with PNPM.

Clinical features	PPM group (n=100)	PNPM group (n=41)	χ^2	P
Age (years), mean±SD	59.2±11.3	61.3±11.7	–0.918	0.360
Male, n (%)	74 (74.0)	30 (73.2)	0.010	0.919
Treatment history, n (%)	57 (57.0)	26 (63.4)	0.494	0.482
Surgery	22 (22.0)	15 (36.6)	3.196	0.074
Chemotherapy	32 (32.0)	12 (29.3)	0.101	0.751
Radiotherapy	24 (24.0)	11 (26.8)	0.125	0.724
Bronchoscopic intervention	15 (15.0)	7 (17.0)	0.095	0.758
Respiratory symptoms, n (%)				
Dyspnea	93 (93.0)	39 (95.1)	0.008	0.929
Cough	82 (82.0)	31 (75.6)	0.726	0.388
Blood-stained sputum	42 (42.0)	16 (39.0)	0.106	0.744
Hoarseness	11 (11.0)	2 (4.9)	0.673	0.412
Stridor	2 (2.0)	4 (9.8)	2.601	0.107
Atelectasis, n (%)	17 (17.0)	1 (2.4)	5.536	0.019
Obstructive pneumonia, n (%)	18 (18.0)	8 (19.5)	0.044	0.833
Stenosis classification, n (%)				
Endoluminal obstruction	0	0		
Extraluminal obstruction	6 (6.0)	10 (24.4)	8.033	0.005
Mixed obstruction	94 (94.0)	31 (75.6)		
Lesion Location, n (%)				
Single central airways involving	37 (37.0)	28 (68.3)		
T	31 (31.0)	28 (68.3)		
RMB	1 (1.0)	0		
LMB	4 (4.0)	0		
BI	1 (1.0)	0		
Multiple central airways involving	63 (63.0)	13 (31.7)	11.459	0.001
T+RMB+LMB	38 (38.0)	11 (26.8)		
T+RMB	13 (13.0)	0		
T+LMB	10 (10.0)	2 (4.9)		
RMB+LMB	1 (1.0)	0		
RBM+BI	1 (1.0)	0		

Data were presented with mean±standard deviation (SD) or n (%). BI: Intermediate bronchus; LMB: Left main bronchus; PNPM: Primary non-pulmonary malignancy; PPM: Primary pulmonary malignancy; RMB: Right main bronchus; T: Trachea.

symptom improvement was achieved. There was no significant difference in symptom improvement rate between the 2 groups (98.0% *vs.* 100.0%; $\chi^2=0.016$, $P=0.898$). The changes in ADI and KPS scores between and within groups are shown in Table 3. Between the 2 groups, ADI before stenting (3.04±0.88 *vs.* 3.20±0.84; $t=-0.966$, $P=0.336$) and after stenting (1.55±0.72 *vs.* 1.55±0.74; $t=-0.082$, $P=0.935$), and KPS scores before stenting (58.70±12.03 *vs.* 57.32±11.41; $t=0.629$, $P=0.530$) and after stenting (76.70±12.48 *vs.* 76.57±12.17; $t=0.050$, $P=0.960$) showed no significant difference. ADI was significantly decreased in the PPM group (3.04±0.88 *vs.* 1.55±0.72; $t=22.661$, $P<0.001$) and PNPM group (3.20±0.84 *vs.* 1.55±0.74; $t=14.268$, $P<0.001$). KPS score was significantly increased in both the PPM (58.70±12.03 *vs.* 76.70±12.47; $t=-20.279$, $P<0.001$) and PNPM (57.32±11.41 *vs.* 76.59±12.17; $t=-15.675$, $P<0.001$) groups.

Complications after stent placement

Bronchoscopic examination was performed within one week of stent placement to evaluate the early complications (≤1 week). Thereafter, bronchoscopic examination was performed every 1 to 3 months or for worsening dyspnea to evaluate late complications (>1 week). If necessary, bronchoscopic intervention was performed to treat the complications. This study was started at the end of the follow-up (December, 2017), or after the patient's last visit to our hospital, or after the patient's death.

Early complications in 120 patients are shown in Table 4. The early development of granulation was mild and did not lead to airway obstruction. Mucosal necrosis and granulation could be removed easily using biopsy forceps. Biopsy forceps were successfully used to adjust four straight stents that migrated. Other early complications were generally mild and reversible, and no endoscopic procedure was required.

A long-term follow-up (median, 86.5 days; range, 9–1749 days) was performed on 62 patients. Late complications are shown in Table 5. Five stents (2 straight; 3 Y-shaped) were fractured after a median of 81 days (range, 32–497 days). Despite this fracture, 4 out of the 5 stents did not compromise airway support. No migration, perforations, or fistulas were observed in late complications. Bronchoscopic intervention (range,

Table 3: ADI and KPS scores of patients with PPM ($n=100$) and patients with PNPM ($n=41$) before and after stenting.

Groups	ADI		KPS scores	
	Before stenting	After stenting	Before stenting	After stenting
PPM group	3.04 ± 0.88	$1.55\pm0.72^{\dagger}$	58.70 ± 12.03	$76.70\pm12.48^{\dagger}$
PNPM group	$3.20\pm0.84^{*}$	$1.55\pm0.74^{\dagger,*}$	$57.32\pm11.41^{*}$	$76.59\pm12.17^{\dagger,*}$

ADI: American Thoracic Society Dyspnea Index; KPS: Karnofsky Performance Scale; PPM: Primary pulmonary malignancy; PNPM: Primary non-pulmonary malignancy. *(between groups) PPM group *vs.* PNPM group, $P>0.05$. †(within group) after stenting *vs.* before stenting, $P<0.05$.

Table 4: Early complications in 120 patients who underwent bronchoscopic examination within one week after stenting.

Early complications	*n* (% in 86 patients with PPM)	*n* (% in 34 patients with PNPM)	*N* (% in 120 patients)
Mucosal necrosis	53 (61.6)	25 (73.5)	78 (65.0)
Increased secretions	54 (62.8)	20 (58.8)	74 (61.7)
Granulation	8 (9.3)	7 (20.6)	15 (12.5)
Bleeding	5 (5.8)	0	5 (4.2)
Migration	3 (3.5)	1 (2.9)	4 (3.3)
Glottic edema	1 (1.2)	1 (2.9)	2 (1.7)

PPM: Primary pulmonary malignancy; PNPM: Primary non-pulmonary malignancy.

Table 5: Late complications in 62 patients who underwent follow-up bronchoscopic examination after stenting.

Late complications	*n* (% in 45 patients with PPM)	*n* (% in 17 patients with PNPM)	*N* (% in 62 patients)
Tumor overgrowth	33 (73.3)	8 (47.1)	41 (66.1)
Mucus retention	23 (51.1)	5 (29.4)	28 (45.2)
Granulation formation	21 (46.7)	5 (29.4)	26 (41.9)
Scar	5 (11.1)	0	5 (8.1)
Fracture	5 (11.1)	0	5 (8.1)
Epithelialization	2 (4.4)	3 (17.6)	5 (8.1)
Bleeding	3 (6.7)	0	3 (4.8)

PPM: Primary pulmonary malignancy; PNPM: Primary non-pulmonary malignancy.

1–6 times) including electrocautery snare (Olympus, Tokyo, Japan), CO_2 cryotherapy (ERBE, Tubingen, Germany), high-frequency electric knife (MTW Endoskopie, Wesel, Germany), argon plasma coagulation (ERBE, Tubingen, Germany), and re-stenting (these methods were used alone or in combination) was performed in 28 patients to deal with the restenosis caused by tumor overgrowth or stent-related complications after stent placement. The patient's exacerbated respiratory symptoms could be relieved to varying degrees after each therapy. In a median period of 131 days after stent placement, the initial bronchoscopic intervention was performed to treat tumor overgrowth (78.6%, 22/28), granulation formation (17.9%, 5/28), and stent fracture (3.6%, 1/28). Two patients underwent re-stenting because stenosis progressed and exceeded the scope of the original stent ($n=1$) and the fractured stent compromised airway support ($n=1$).

Removal of 2 stents after placement (80 days and 88 days) was attempted because of disease improvement after chemotherapy ($n=1$) and because of stent fracture ($n=1$). Both attempts failed because the stents were embedded in the airway mucosa.

Discussion

PPMs are the main cause of malignant CAO requiring stent placement. The proportion of patients with PPM in this study was 70.9%; squamous cell carcinoma, adenocarcinoma, and adenoid cystic carcinoma were the most common histological types. PNPMs that cause malignant CAO could originate from mediastinal or extrathoracic organs, such as the esophagus, thyroid, lymph, liver, and kidney. Some rare conditions, such as primary or metastatic malignant melanoma, involving the airways may also develop.[5,6] Due to the lack of specificity of respiratory symptoms, patients with malignant CAO are sometimes misdiagnosed with asthma or chronic obstructive pulmonary disease.[3] In this study, similarities in respiratory symptoms and patient characteristics (age, sex) were observed. Before stent placement, the patients with CAO caused by PPM and PNPM had poor performance statuses and most of them had a treatment history including surgery, chemotherapy, radiotherapy, and bronchoscopic intervention (patients received at least 1 treatment method). Malignancies can cause airway stenosis either by external compression or

direct tumor growth into the airways, while extrathoracic cancers can metastasize to the airways.[3] In this study, esophageal and thyroid cancers were the most common PNPMs, and both were adjacent to the airway. They could directly infiltrate and grow into the airway, especially the trachea. Sometimes, although they did not break through the airway wall, their expansive growth resulted in compression of the airway. This was why single airway involvement and extraluminal obstruction (especially in the trachea) were more common in malignant CAO caused by PNPM. Patients with PPM were more likely to have atelectasis. Unlike PNPM, PPM was more likely to involve bronchial and/or smaller airway branches. Atelectasis of the pulmonary lobe or segment due to complete obstruction of these airways was generally nonfatal and tolerable, thus delaying the diagnosis and treatment. In addition, bronchoscopic intervention in these relatively smaller airways is difficult. This may explain why atelectasis was more common in patients with PPM.

When patients require stent placement for malignant CAO, they have often exhausted other treatments or they need rapid relief from life-threatening airway obstruction. Bronchoscopic intervention including laser, electrocoagulation, argon plasma coagulation, and cryotherapy has been proven to be a safe and effective palliative treatment for intraluminal tumors, specifically to maintain lumen patency.[7,8] Stent placement can be delayed or even avoided by interventional therapy. However, bronchoscopic intervention is not suitable for extraluminal obstruction, and its usefulness in the case of mixed obstruction is limited. In these cases, stent placement should be considered.

Currently, a variety of airway stents are available for malignant airway stenosis.[2,9-11] The heterogeneity of different types of airway stents limits the generalizability of the research results. The Micro-Tech stents used in this study were self-expandable nitinol metallic stents. They are available in straight and bifurcated shapes and have the feature of customizability. Straight stents are suitable for placement in the trachea or large bronchi. When dealing with airway lesions that are near the carina, bifurcated Y-shaped stents are preferable. Due to their good shape adaptability and expansion force, the Micro-Tech stents are appropriate for use in complex stenosis with airway distortion.

In this study, the symptom improvement rate and the improvements in ADI and KPS scores were the same in patients with malignant CAO caused by both PPM and PNPM. Stent-related complications were nonfatal and could be effectively managed by bronchoscopic procedures. Mucosal necrosis was the common change in the early stage, which generally developed at the ends of the stents or in the areas of airway lesions. This may be related to the greater tension between the airway mucosa and stent in these areas. The necrotic tissues could be easily removed by biopsy forceps. Granulation is one of the major complications of metal stents, and lower respiratory tract infections may increase the risk of the granulation.[12] Epithelialization is uncommon but not rare and may develop a few weeks after uncovered or partially covered metal stent placement.[13] In this study, stent migrations were only observed in early rather than late complications. This was probably because as the stent became embedded in the airway mucosa after placement for a period of time, tumor granulation tissue or epithelialization developed holding it in place. The most common reason for performing bronchoscopic procedure after stent placement in this study was restenosis caused by tumor overgrowth. In situations wherein stenosis progresses over the edge of the original stent or stent fracture compromises airway support, re-stenting is still considered useful to improve dyspnea.[14]

Uncovered metal stent removal is difficult and risky.[15,16] Granulation, epithelialization and tumor overgrowth are all disadvantages for stent removal. Stent removal is only considered in a small number of patients with malignant CAO, and the indications mainly include disease improvement after tumor-specific treatment or development of serious stent-related complications. It is more suitable to insert temporary stents in patients with malignant airway stenosis that is sensitive to tumor-specific treatment.[17,18]

In this study, most patients were referred from other hospitals that were distant from our hospital. When the patients were too sick to tolerate long-distance travel to our hospital, they often visited their local hospitals and did not return to ours. Therefore, we rarely recorded the patient's survival time. Previous studies showed that the prognosis after stent placement was poor because the initial disease was advanced and aggressive.[19,20] Longer survival times are associated with tumor-specific treatment after stent placement.[7,20]

In conclusion, in malignant airway stenosis requiring stent placement, those caused by PPM are more likely to involve multiple airways and are associated with atelectasis, while those caused by PNPM are more likely to cause extraluminal obstruction. Micro-Tech stent placement has the same immediate effect in improving the symptoms and performance status and, in combination with bronchoscopic intervention, can provide a safe and effective palliative treatment for patients with malignant airway stenosis caused by both PPM and PNPM.

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Conflicts of interest

None.

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