

Mucoepidermoid Tumors of the Lung: Analysis of 11 Cases

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Key Words

bronchial adenoma;
histological grading;
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Background. Mucoepidermoid tumors (METs) of the trachea and bronchi are rare. They derive from the minor salivary gland tissue of the proximal tracheobronchial tree, and their clinical behaviors are still controversial. Herein, we analyze 11 cases of MET to investigate its clinicopathological characteristics.

Methods. The medical records and pathological examinations of patients diagnosed with MET from May, 1995 to May, 2001 at the Division of Thoracic Surgery in Taipei Veterans General Hospital were retrospectively reviewed.

Results. There were 11 patients (7 male and 4 female) aged from 19 to 79 years, with a peak at the seventh and eighth decade. The mean age at diagnosis was 58.9 years, and 9 of these 11 patients were symptomatic. No surgical mortality occurred. Three patients with low-grade tumors were all young females (less than 30 years). They were all alive without evidence of disease recurrence until the date of analysis, whereas the 5-year survival of 8 patients with high-grade tumors was only 25%. Six patients with high-grade tumors received adjuvant therapy, but their prognoses remained poor.

Conclusions. In the current study, METs occurred more frequently in male patients. Young female patients were preponderant to have low-grade tumors and therefore associated with better prognosis. Histological grading of the MET and the ability to achieve an anatomic resection are 2 most important factors that affect prognosis. Adjuvant therapy seems not to be effective in patients with high-grade MET.

Mucoepidermoid tumors (METs) of the trachea and bronchi were first described in 1952 by Smetana *et al*¹ and Liebow.² The understanding of the nature of these tumors has undergone an interesting evolution. Initially, they were recognized as only occurring in the salivary gland but later some appreciated that they occurred in the trachea and bronchi as well.^{3,4} Early studies of MET of the tracheobronchial tree included them under the category of bronchial adenomas together with carcinoid tumors and adenoid cystic carcinomas (cylindromas).⁵ This indicated that they were essentially benign tumors confined to the bronchus and occasionally metastasized to lung and lymph nodes. Later studies, however, recognized a clearly malignant type of MET which had a high propensity for metastases.⁶

Histologically, these tumors are similar to those originally described in the major salivary glands and are be-

lieved to originate from the minor salivary glands lining the tracheobronchial tree. According to some established gross, histological and ultrastructural criteria, these tumors were divided into high-grade and low-grade groups.⁷ However, it has been reported that "low-grade" MET of the bronchus could be associated with "high-grade" biological behaviors.⁸

So far, only few MET cases have been reported in Taiwan. Herein, we retrospectively analyze 11 patients with METs, and emphasize the clinical features, histopathological findings, treatment results and possible prognostic indicators.

METHODS

From May, 1995 to May, 2001, 11 patients diag-

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nosed with MET of lung at the Division of Thoracic Surgery in Taipei Veterans General Hospital were retrospectively analyzed. All of them underwent surgical intervention, and the preoperative work-up consisted of blood cell test, biochemistry studies, chest radiography and computer tomography (CT scan), and bronchoscopic examinations. Their medical records, operative procedures, and follow-up data were thoroughly reviewed. According to mitotic activity, cellular necrosis and nuclear pleomorphism upon histological examination, each tumor was classified as low-grade or high-grade.

Survival of patients was plotted, and median survival was estimated by the Kaplan-Meier method. Survival difference was compared with the log-rank test.

RESULTS

Clinical features

There were 7 male and 4 female patients. Their mean age at diagnosis was 58.9 years, ranging from 19 years to 79 years (Table 1). Four patients were diagnosed at the seventh decade and another 4 patients at the eighth decade. Interestingly, the remaining 3 patients were all young females (less than 30 years). Five patients had smoking habit and were all males. The presenting symptoms included productive cough (4 patients), hemoptysis (2 patients), recurrent pneumonia (2 patients), and dry

cough (1 patient). Two patients were asymptomatic.

The chest radiographs of these 11 patients were all abnormal. A mass lesion was usually easy-recognized, and sometimes accompanied by atelectasis. Only 1 patient presented with a vague mass lesion but patchy infiltration over left lower lobe. Of the 10 patients with mass lesions, 3 had a central 1. The tumor size ranged from 1.5 cm to 9 cm. Of interest, 1 had a marked air-fluid level within the mass, and was later proved to be caused by tumor necrosis.

Bronchoscopic examinations were performed for all patients. Three patients did not show abnormality. Two patients had luminal obstruction caused by endobronchial tumors, and 5 patients had the picture of external compression. Mucosal erosion of right main bronchus was found in 1 patient. All patients with abnormal bronchoscopic findings had a positive result for malignancy with endoscopic biopsy or brushing cytology.

Pathological findings

The largest diameter of resected tumors sized from 2 to 9 cm. Upon section, these tumors were gray-white in color. Pathologically nuclear pleomorphism was evaluated in terms of degree of hyperchromatism, clumping of chromatin, and enlargement of nucleoli. Three tumors had slight nuclear polymorphism, 4 had moderate nuclear polymorphism and 4 had marked nuclear polymorphism. Those with marked nuclear polymorphism also

Table 1. Clinical Data of the 11 patients with MET

Pt	Sex	Age	Sym	Smo	Loc	Pre-op Dx	Bronch	Op	Stage	Gr	C/T, R/T	Rec	Sur
1	M	75	PC	Y	RUL	Tm	Ex Com	LOB	T ₁ N ₀ M ₀	H	+	-	+
2	F	24	Pn	N	LLL	Tm	TO	LOB	T ₁ N ₀ M ₀	L	-	-	+
3	M	67	Nil	Y	RLL	Pn	Ex Com	LOB	T ₂ N ₀ M ₀	H	+	-	+
4	M	68	PC	Y	LLL	Pn	Nor	LOB	T ₁ N ₀ M ₀	H	+	-	+
5	F	19	He	N	LUL	Tm	Nor	SEG	T ₁ N ₀ M ₀	L	-	-	+
6	F	78	DC	N	RML	Tm	Ex Com	WED	T ₂ N ₀ M ₀	H	+	+	-
7	M	67	Nil	N	RUL	Ate	Ex Com	SL LOB	T ₂ N ₂ M ₀	H	+	+	-
8	M	76	Pn	N	LUL	Tm	TO	LOB	T ₂ N ₀ M ₀	H	+	+	-
9	M	66	PC	Y	RUL	Tm	Ex Com	LOB	T ₂ N ₂ M ₀	H	+	+	-
10	F	29	He	N	RLL	Tm	Nor	LOB	T ₂ N ₀ M ₀	L	-	-	+
11	M	79	PC	Y	LLL	Tm	Ex Com	WED	T ₂ N ₀ M ₀	H	+	+	-

Ate = atelectasis; Broncho = bronchoscopic finding; DC = dry cough; Ex com = external compression; F = female; Gr = grading; H = high grade; He = hemoptysis; L = low grade; LLL = left lower lobe; LOB = lobectomy; LUL = left upper lobe; M = male; Nor = normal; PC = productive cough; Pn = pneumonia; Rec = recurrence; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SEG = segmentectomy; SL LOB = sleeve lobectomy; Smo = smoking; Sur = survival; Sym = symptom; TO = tumor occlusion; Tm = tumor; WED = wedge resection.

had more extensive mitotic activity and necrosis. On the basis of mitotic activity, cellular necrosis and nuclear pleomorphism, we classified these tumors into high-grade (8 patients) and low-grade (3 patients).

Microscopically, the low-grade METs had a mixed solid and cystic appearance with sheetlike epidermoid areas separated by mucus-filled cysts of irregular size (Fig. 1). Areas of solid growth were composed of squamoid and intermediate cells; the former were polygonal cells with a homogeneous hyaline eosinophilic cyto-

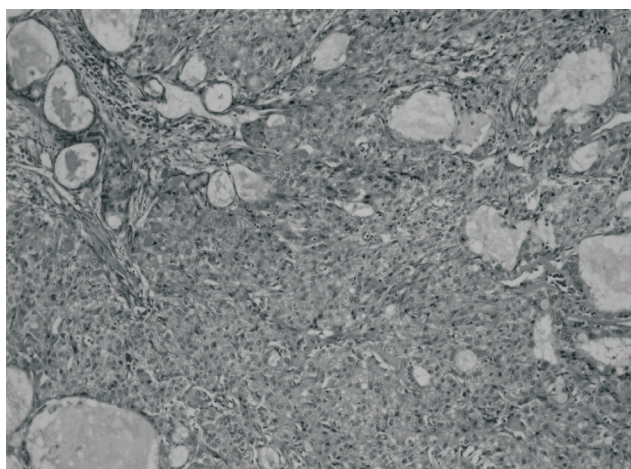


Fig. 1. Low-grade MET. The tumor is composed of solid sheetlike areas of squamoid cells (lower part) and mucin-rich goblet cells and low cuboidal, mucin-pool cells surrounding pools of mucus (upper part). (Hematoxylin and eosin, X100).

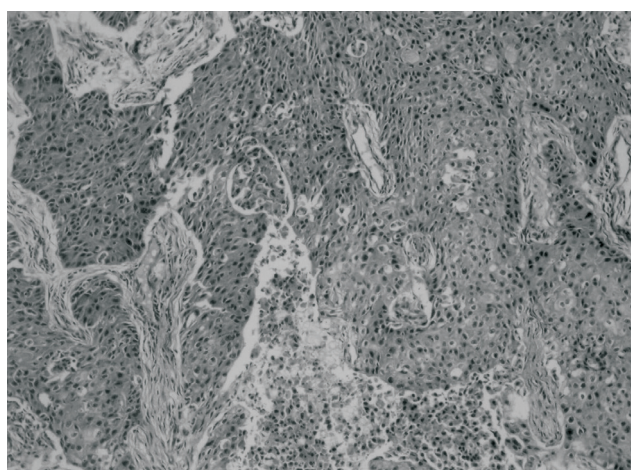


Fig. 2. High-grade MET. The tumor contains both a solid and a glandular component and irregularly infiltrates the surrounding tissue. Necrosis was also noted (lower part). (Hematoxylin and eosin, X100).

plasm, whereas the latter were oval cells with a round nucleus and faintly eosinophilic cytoplasm. Cysts were lined only by columnar or goblet cells, with the latter usually filled with bubbly mucin-rich cytoplasm.

On the other hand, the high-grade METs contained both a solid and a glandular component, with the former constituting most of the tumors (Fig. 2). The solid area consisted of cells somewhat smaller than those seen in the low-grade tumor. Most tumors showed a moderate degree of cellular and nuclear pleomorphism. The nuclei showed significant variation in appearance, with both hyperchromatic nuclei and vesicular nuclei containing prominently small nucleoli. Foci of necrosis were frequently seen.

All of 8 high-grade tumors had involvement of lung parenchyma, whereas the 3 low-grade tumors confined to bronchial wall and were polypoid in gross appearance. Half of the high-grade tumors, invaded the visceral pleura without penetrating it. Tumor necrosis was characteristic of high-grade tumors, and 7 high-grade tumors had such findings under microscopic examination.

Lymph node metastasis was noted in 2 high-grade tumors, and both had mediastinal (N2) lymph node involvement. Interestingly, both of them were right upper lobe tumors. Whether visceral pleura invasion was a determinant of lymph node metastasis remained questionable, because only 1 N2 tumor had visceral pleura invasion at tumor site.

Treatment

All patients underwent exploratory thoracotomy, and there was no surgical mortality. Three tumors were at right upper lobe, 1 tumor at right middle lobe, 2 tumors at right lower lobe, 2 tumors at left upper lobe, and 3 tumors at left lower lobe. Operative modes included 7 lobectomies, 1 sleeve lobectomy, 1 segmentectomy and 2 wedge resections. One patient who had received a right lower lobectomy for squamous cell carcinoma 14 months earlier had undergone a wedge resection of left lower lobe. Another wedge resection was performed since low possibility of malignancy was reported at frozen section examination. Tumors were all resectable and only 1 patient did not undergo radical lymph node dissection because of poor cardiopulmonary reserve. The bronchial cut-margins of the patients were all mi-

croscopically negative.

No further treatment was applied to those patients with low-grade tumors. Six of 8 high-grade MET patients received adjuvant therapy due to advanced tumor stages (2 patients), limited resection (3 patients) or huge tumor size (1 patient). One patient with suspected regional lymphadenopathy during preoperative evaluation received neoadjuvant chemotherapy, followed by post-operative adjuvant chemoradiotherapy, after lymph node metastasis was documented pathologically. The adjuvant chemotherapy regimens consisted of Navelbine and Gemcitabine.

Survival

The 3 young females with low-grade tumors were all alive without evidence of disease recurrence until the time of study. However, the median survival of the 8 patients with high-grade tumors was only 23.5 months. Meanwhile, the 5-year survival of these 8 patients was about 25%. Nevertheless, the survival difference between these 2 groups was not statistically significant ($p = 0.12$) (Fig. 3), which might be the inadequate number of cases for survival analysis.

Until the time of this study, 5 patients with high-grade tumors succumbed. The causes of death included: respiratory failure (1 patient), local tumor recurrence (2 patients), systemic metastasis (1 patient) and multiple brain metastases (1 patient). The patient who underwent

a sleeve lobectomy died of respiratory failure 4 months after surgery. The patient who received a right lower lobectomy for squamous cell carcinoma 1 year earlier underwent only wedge resection of left lower lobe. He had tumor recurrence clinically and received a second wedge resection of left lower lobe 2 years later. Finally, he died of pneumonia and respiratory failure 1 year after the second operation. Another patient who received a wedge resection were also dead 1.5 years after a second tumor resection for local recurrence. A patient with N2 disease died of carcinomatosis 1.5 years after operation. The other patient with multiple brain metastases expired due to central failure 6 months postoperatively, despite the treatments of Gamma-knife and whole brain irradiation.

DISCUSSION

The submucosa of trachea and bronchial upper airway and the salivary glands contain serous and mucous glands that are histologically similar.^{7,9} Tumors arising from these glands, regardless of the location, also share resembling histology and biological activity. Mucoepidermoid tumors of the salivary gland, the most common malignancies in those tissues, were first described distinctly by Stewart *et al* in 1945.¹⁰ After the earliest description, debate and controversy existed as to the malignant potential of these tumors. They were designated as mucoepidermoid tumors in the 1972 World Health Organization (WHO) classification,¹¹ and once fell into an uncommitted diagnostic category between adenomas and carcinomas. Currently, most authors agree that they are malignant, as is reflected in the revised WHO classification of mucoepidermoid carcinoma.

Mucoepidermoid tumors of the trachea and bronchi are instead quite uncommon, constituting 1% to 5% of bronchial adenomas and 0.1% to 0.5% of all lung tumors. They can occur over a broad range of age, including childhood.¹³⁻¹⁵ The mean age in the present study is 58.9 years, which is much older than those in pervious reports. In 2 larger series, Heitmiller *et al.* reported a mean age of 36.8 years in 18 patients¹⁶ and Yousem *et al.* reported a mean age of 34.8 years in 45 low-grade METs as well as a mean age of 44.5 years in 13 high-grade METs.¹⁷ The exact cause of this difference is still un-

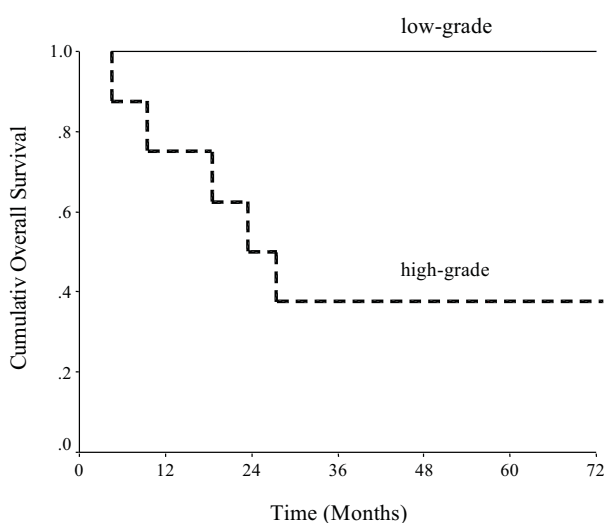


Fig. 3. Survival curves of patients with high-grade and low-grade METs. ($p = 0.12$).

known. However, since high-grade METs usually occur in older patients, it is not surprising that the mean age in our series is older because high-grade METs account for the majority of our patients.

Although some have reported a male predominance, most studies fail to demonstrate a clear predilection based on gender. In our series, there were 7 male and 4 female patients. Since the patient number is not large enough, it is difficult to make conclusion on this issue. Meanwhile, we found only 5 male patients had smoking habits, and as in previous reports,^{16,17} the relationship between this tumor and smoking habit is not obvious.

It has been found that low-grade METs occur more frequently in younger patients.¹⁷ Our findings were consistent with this characteristic, and we further noticed that the low-grade METs had a female predominance. The 3 patients with low-grade MET in our series were all younger than 30 years of age. This evidence could be related to female hormone status, but further investigation is needed.

Symptoms are primarily those of bronchial irritation and obstruction, and include cough, hemoptysis and postobstructive pneumonia. In previous reports, symptoms were similar in low-grade and high-grade groups. In the current series, productive cough is the most common symptom, followed by hemoptysis, recurrent pneumonia and dry cough. Two patients were asymptomatic, and both of them had high-grade MET. All 3 patients with low-grade MET were symptomatic, including 2 with hemoptysis and 1 with recurrent pneumonia.

Because mucoepidermoid carcinomas are most commonly found in the segmental or lobar bronchi and symptoms of airway irritation or obstruction are common, bronchoscopic examination for diagnosis is essential. In the current study, bronchoscopic examinations were performed for all patients. Three of them were normal, and this may be a little different from the study reported by Heitmiller *et al.*,¹⁶ which showed 100% positive rate in 18 patients.

Unlike the salivary gland counterparts, which are usually adapt to a 3-grade system,¹⁸ METs of trachea and bronchi are divided into low-grade or high-grade lesions. This distinction is based on nuclear pleomorphism, mitotic activity and the presence of necrosis. Necrosis was found only in high-grade MET, and mitoses including

atypical activity were also restricted to them. In the current study, histological grading seems to correlate with prognosis well. All 3 patients with low-grade MET are still alive well, but the median survival of 8 patients with high-grade MET was only 23.5 months. Although the survival difference is not statistically significant, this is probably due to small number of our patients. In addition, our 8 patients with high-grade MET seem to have poor survival than ever reported, for which tumor aggressiveness itself might count. All of these 8 tumors had involvement of lung parenchyma, and therefore exhibited a more malignant behavior.

Surgery is the treatment of choice for patients with MET because there is no report of long-term survival in patients who are not treated surgically. Therapeutically, low-grade tumors should be completely excised, and lobectomy with complete locoregional lymph node dissection is usually the most expeditious choice. Compared with other series, we find our procedures were relatively less aggressive. In the report of Heitmiller *et al.*, lobectomies were performed in only 5 of 16 patients with resectable diseases and the other 11 patients underwent bilobectomies, sleeve resection or pneumonectomy. We suppose this is because our patients have less central lesions. Nevertheless, wedge or segmental resection is definitely not sufficient for the high-grade METs. In the current series, 2 patients underwent such inadequate procedures had both local recurrence a few years later.

Postoperative radiotherapy or chemotherapy is probably unnecessary for low-grade MET. In our study, adjuvant therapy had been prescribed to 6 patients with high-grade MET for different indications. Despite these treatments, 5 patients died with tumor recurrence or distant metastases, and only 1 is still alive until the date of data analysis.

In conclusion, METs occur more frequently in male patients, and young female patients are preponderant to have low-grade tumors. Histological grading of MET and the ability to achieve an anatomic resection are 2 factors that affect prognosis. Patients with low-grade MET who underwent complete resections had excellent long-term survivals. However, adjuvant therapy shows no effect on patients with advanced high-grade MET or in patients who are not adequately resected.

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