Primary salivary gland-type tumors of the lung: A systematic review and pooled analysis

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ABSTRACT

Introduction: Primary salivary gland-type tumors of the lung (PSGTTL) are rare intrathoracic malignant neoplasms. Their description in literature is largely limited to a few case series and case reports. A systematic review and pooled analysis of the previously reported cases of PSGTTL is presented here. Methods: Electronic database of PubMed using keywords “lung neoplasm” AND “salivary gland tumors” was used to identify the papers documenting the PSGTTL. Filters (publication date from January 1, 1900—December 31, 2015, Humans and English) were applied to refine the search. A pooled analysis of clinical, pathological, treatment, and survival data was performed. Results: The present systematic review included 5 studies and a total of 233 patients. Mean age of the patients was 41 years (range 6–80 years) and there was a male preponderance (1.3:1). Common pathological types were mucoepidermoid (MEC) (56.6%), adenoid cystic (ACC) (39.5%), and epithelial-myoepithelial cancer (3.8%). Tumors were located in the central airways (trachea and major bronchi) in 43.3% of patients. Weighted median tumor size was 4.2 cm. Surgery was the primary treatment undertaken in 82.4% of the patients, while radiotherapy and chemotherapy were also used in 15.9% and 9.4% of the patients. Lymph node involvement was seen in 15.2% of the patients. Disease recurrences were observed in 21.1% of the patients (12.9% and 37.5% in MEC and ACC, respectively). Three-, 5-, and 10-year weighted overall survival was 86.4%, 81.4%, and 73.6% (93.8%, 90.0%, and 85.0%, respectively, for MEC and 76.7%, 62.8%, and 50.5%, respectively, for ACC). Conclusion: Surgery is the primary treatment of PSGTTL to achieve long-term survival. Role of chemotherapy and radiotherapy in the management of PSGTTL warrants further studies.

KEY WORDS: Adenoid cystic cancer, lung neoplasms, mucoepidermoid cancer, pooled analysis, salivary gland neoplasms

INTRODUCTION

Salivary-type neoplasms are known to occur at multiple organ sites in view of the basic structural homology among the exocrine glands in these anatomic sites. Primary salivary gland-type tumors of the lung (PSGTTL) are rare intrathoracic malignant neoplasm constituting <1% of all pulmonary tumors.1 They are histologically not indifferent from their counterparts of salivary origin; they are thought to arise from the submucosal glands of the tracheo-bronchial tree.2-3 The two common histological types of PSGTTL are mucoepidermoid cancer (MEC) and adenoid cystic cancer (ACC) and a rare type is epithelial-myoepithelial cancer (EMC).2,4-6 Their description in literature is largely limited to a few case series and case reports. A greater awareness of PSGTTL is essential for accurate diagnosis and proper clinical management. A systematic review and pooled analysis of the previously reported cases of PSGTTL is presented here for a better understanding of this rare entity.

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their frequency of occurrence, clinical behavior, treatment options, pathologic features, and outcome.

**METHODS**

We searched the electronic database of PubMed using the key words "lung neoplasm" AND "salivary gland tumours" to identify the papers documenting the PSGTTL. Filters (publication date from January 1, 1900–December 31, 2015, Humans, and English) were applied to refine the search. All the articles which were single case reports or had exclusively presented one pathological type of PSGTTL were not included in the review.

A pooled analysis of the clinical, pathological, treatment-related, and survival data was performed. All the relevant data were entered into a personal computer on Microsoft Excel sheet and analyzed. While doing the pooled analysis, weighted average of the individual summary statistics was calculated. Mean was estimated from the median and range using the formula reported by Hozo et al. 

**RESULTS**

Initial PubMed search, using the stated keywords, yielded 481 articles. After applying the necessary filters, 349 articles were identified. A careful search of references in the articles was carried out to identify other relevant articles [Figure 1]. Five studies satisfying the inclusion criteria were included in the present review [Table 1]. A pooled analysis of the 233 patients included in these studies was carried out.

**Clinical presentation**

Median age reported in the studies ranged from 41.5 to 51 years [Table 1], and mean age of the patients after pooled analysis was 41 years (range 6–80 years). In all but one study, there was disease preponderance to male sex with male-to-female ratio ranging from 0.8 to 1.8. Pooled analysis showed a male preponderance (1.3:1). In the two largest studies reported on the topic by Molina et al. [3] and Zhu et al., [4] the most common symptom was cough [Table 1]. Dyspnea and hemoptysis were also common.

**Pathological data**

Common pathological types were MEC (56.6%), ACC (39.5%), and EMC (3.8%). For the purpose of statistical analysis, MEC and EMC were considered as a single group. Tumors were located in the central airways (trachea and major bronchi) in 43.3% of the patients. Weighted median tumor size was 4.2 cm.

**Management**

Surgical resection was the preferred management option in all the studies (71%–100% of cases). Adjuvant therapy, either chemotherapy or radiotherapy, was variably used in these studies. The pooled analysis showed that surgery was the primary treatment undertaken in 82.4% of the patients, while radiotherapy and chemotherapy were used in 15.9% and 9.4% of the patients, respectively. Among the surgical procedures, lobectomy was performed in 14.2%–55.7%, pneumonectomy in 14.6%–71%, and tracheal resection in 16.7%–25.6% of the cases [Table 2]. Lymph node involvement was seen in 15.2% of the patients.

**DISCUSSION**

PSGTTL are extremely rare tumors of the lung arising from the associated serous and mucous glands of the respiratory tract. [1] In the present review, the common types of PSGTTL, i.e., MEC and ACC were focused on. It usually affects the patients in their middle age, with the mean age of diagnosis being 41 years. ACC affects a slightly older population (50 years vs. 42 years) as compared to MEC. Zhu et al. [4] and Elnayal et al. [8] reported no difference in terms of age in the two pathological types, whereas Molina et al. [3] reported a significantly higher age for ACC (40 vs. 54, P = 0.02). A wide variation in the ages affected was reported by Molina et al. [3] Zhu et al. [4] and Kang et al. [9] in their studies [Table 1]. PSGTTL shows a slight male preponderance with a ratio of 1.3:1. All the studies except one showed a male predilection for
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PSGTTL; Elnayal et al.[8] reported a male-to-female ratio skewed toward the female sex.

The pooled analysis [Table 4] shows MEC to be the most common pathological type (56.6%) followed by ACC (39.5%) and EMC (3.8%). Of the studies included in the review, Molina et al.[3] and Pandey et al.[9] reported a higher percentage of ACC. Admittedly, our pooled data are skewed toward MEC because of the inclusion of study by Zhu et al.[4] which reported MEC to be present in 78.4%, while ACC in 13.6% of the 88 cases. Different studies report a wide variation in the tumor size and location. The size of the tumor varied from 0.5 to 12 cm. However, the pooled analysis did not show any difference in tumor size between the two histopathological types. The tumor location in PSGTTL has been reported to be central airways in 15.9%–100% of the cases. ACC appears to be more centrally located compared to MEC (61.3% vs. 26.5%). The clinical manifestation is largely decided by the tumor location and the presence of the distal obstruction. Majority of the patients present...
with cough and dyspnea; other clinical symptoms are hemoptysis, wheezing, or obstructive pneumonitis. Complete surgical resection with negative margins is the preferred treatment for a resectable PSGTTL. To fulfill this goal, a wide variety of procedures were performed in different case series varying from sleeve resections to lobectomies and pneumonectomies. Majority of the patients in the series reported by Pandey et al.\(^\text{[9]}\) had a pneumonectomy to achieve margin negative resection. The authors contributed this to the central location and locally advanced nature of tumor in their patients. The authors further elaborated that majority of their patients were initially misdiagnosed as having tuberculosis and prescribed antituberculosis therapy, leading to a delay in the correct diagnosis of PSGTTL.

Yousem and Hochholzer divided MEC based on pathological grades into low and high grades.\(^\text{[10]}\) Low-grade tumors were reported to have better survival, whereas high-grade tumors had higher rates of recurrence, lung parenchymal invasion, and mortality. Zhu et al.\(^\text{[4]}\) reported that the pathological grade was a significant predictor of OS (hazard ratio [HR]: 0.045; 95% confidence interval [CI]: 0.005–0.410; \(P = 0.006\)) as well as disease-free survival (HR: 0.067; 95% CI: 0.013–0.337; \(P = 0.001\)) for patients with MEC. Molina et al.\(^\text{[3]}\) also reported the correlation of grade with tumor invasion, with almost 50% of high-grade tumors showing lung parenchymal invasion. They also reported a better survival in low-grade tumors, which was not found to be statistically significant. Kang et al.\(^\text{[30]}\) did not find any difference in low- and high-grade tumors in terms of lymph node involvement and survival but suggested a close follow-up of the patients with high-grade MEC. The role of adjuvant therapy in an optimally resected MEC is not well defined. Though it is clear that low-grade MEC does not require any adjuvant therapy after a margin-free resection, whether a high-grade MEC requires an adjuvant therapy remains an unanswered question and warrants further studies.\(^\text{[11]}\) Active surveillance must be ensured in the follow-up period to detect early salvageable recurrences. ACC commonly extends beyond the visible gross tumor due to submucosal spread and perineural invasion, leading to higher rates of margin positivity and disease recurrence compared to MEC. The patients with ACC are at a higher risk (relative risk [RR]: 4.19, 95% CI: 1.59–11.02; \(P < 0.01\)) of death compared with patients who had MEC; the risk remains nearly 3 folds even after adjusting for age.\(^\text{[31]}\) The pooled analysis of the PSGTTL in the present study highlighted a disease recurrence in 37.5% of the patients with ACC.

The role of lymphadenectomy is still not clear in the management of PSGTTL because of the low frequency of lymph nodal involvement varying from 0% to 20% in different studies. The pooled analysis shows no difference in the lymph node involvement among the patients with either type of tumor. At present, lymphadenectomy may be limited to patients with grossly visible lymph nodes as suggested by previous studies, until robust data from prospective studies provide evidence to support lymphadenectomy in all cases. Presently, there is scarcity of data to define the indications of adjuvant therapy in the management of PSGTTL. Though adjuvant radiotherapy is being advised in patients with positive surgical margins, its true benefit is not known. The rarity of the condition makes it unfeasible to conduct good quality randomized controlled trials to answer these questions. A pooled analysis of patient data from various centers or a case registry may help clear the air about many of the management issues.

PSGTTL are generally considered slow growing and rarely present with metastasis at the first presentation. The OS has been better for MEC as compared to ACC. The pooled analysis suggests a 3-year survival of 86.4%, which is similar to the results of the previous studies. The mean 5- and 10-year survival was 81.4% and 73.6%, respectively. Molina et al.\(^\text{[3]}\) reported inferior 5- and 10-year OS rates due to larger number of cases with ACC (64.5%). Zhu et al.\(^\text{[4]}\) and Kang et al.\(^\text{[3]}\) reported slightly better OS as they had a larger share of cases with MEC.

**Table 4: Pooled analysis of patients of primary salivary gland-type pulmonary tumors**

| Characteristics | Total (n=233) | MEC+EMC (n=141) | ACC (n=92) |
|-----------------|--------------|-----------------|------------|
| Mean age        | 41.4         | 42.1            | 50         |
| Gender (male: female) | 1.3          | 1.4             | 1.42       |
| Location (central airways) (%) | 43.3         | 26.5            | 61.3       |
| Mean size (cm)  | 4.2          | 4.2             | 4.1        |
| Lymphadenopathy (%) | 15.2         | 15.6            | 14.6       |
| Mean size (cm)  | 4.2          | 4.2             | 4.1        |
| Disease recurrence (%) | 21.2         | 12.9            | 37.5       |
| 3-year OS (%)   | 86.4         | 93.8            | 76.7       |
| 5-year OS (%)   | 81.4         | 90.0            | 62.8       |
| 10-year OS (%)  | 73.6         | 85.0            | 50.5       |

OS: Overall survival, ACC: Adenoid cystic carcinoma, MEC: Mucoepidermoid carcinoma, EMC: Epithelial-myoepithelial carcinoma

**CONCLUSION**

Margin-negative radical resection is the mainstay of treatment of PSGTTL to achieve long-term survival. Disease recurrences are more common with ACC as compared to MEC with poor long-term survival. The role of chemotherapy and radiotherapy in the management of PSGTTL warrants further studies.

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**Conflicts of interest**
There are no conflicts of interest.

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REFERENCES

1. Heitmiller RF, Mathisen DJ, Ferry JA, Mark EJ, Grillo HC. Mucoepidermoid lung tumors. Ann Thorac Surg 1989;47:394-9.
2. Moran CA, Suster S, Koss MN. Primary adenoid cystic carcinoma of the lung: A clinicopathologic and immunohistochemical study of 16 cases. Cancer 1994;73:1390-7.
3. Molina JR, Aubry MC, Lewis JE, Wampfler JA, Williams BA, Midthun DE, et al. Primary salivary gland-type lung cancer: Spectrum of clinical presentation, histopathologic and prognostic factors. Cancer 2007;110:2253-9.
4. Zhu F, Liu Z, Hou Y, He D, Ge X, Bai C, et al. Primary salivary gland-type lung cancer: Clinicopathological analysis of 88 cases from China. J Thorac Oncol 2013;8:1578-84.
5. Kang DY, Yoon YS, Kim HK, Choi YS, Kim K, Shim YM, et al. Primary salivary gland-type lung cancer: Surgical outcomes. Lung Cancer 2011;72:250-4.
6. Moran CA. Primary salivary gland-type tumors of the lung. Semin Diagn Pathol 1995;12:106-22.
7. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
8. Elnayal A, Moran CA, Fox PS, Mawlawi O, Swisher SG, Marom EM, et al. Primary salivary gland-type lung cancer: Imaging and clinical predictors of outcome. AJR Am J Roentgenol 2013;201:W57-63.
9. Pandey D, Garg PK, Jakhetiya A, Pandey R, Bhorwal S, Nath D, et al. Surgical experience of primary salivary gland tumors of lung: A case series. Int J Surg 2015;21:92-6.
10. Yousem SA, Hochholzer L. Mucoepidermoid tumors of the lung. Cancer 1987;60:1346-52.
11. Conlan AA, Payne WS, Woolner LB, Sanderson DR. Adenoid cystic carcinoma (cylindroma) and mucoepidermoid carcinoma of the bronchus. Factors affecting survival. J Thorac Cardiovasc Surg 1978;76:369-77.