Original Article

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

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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] 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).[2-6] 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

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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*.[7]

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[3-5,8,9] 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.

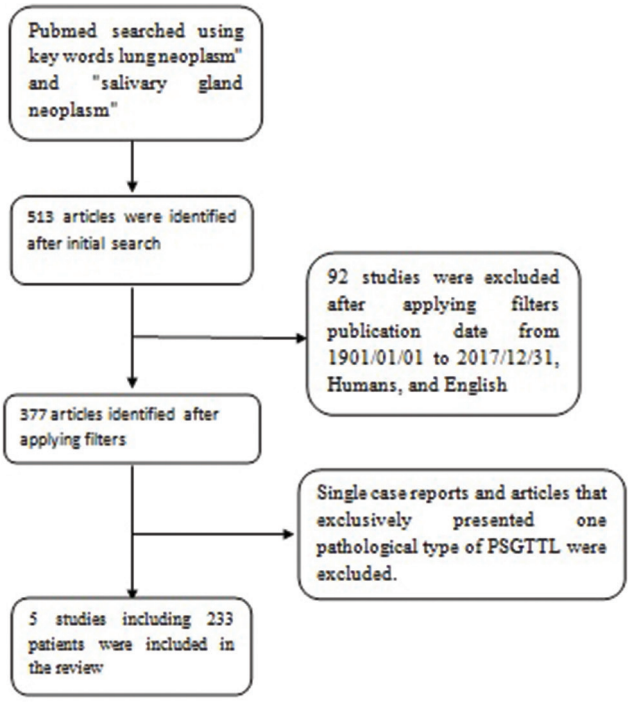

Figure 1: PRISMA flow diagram depicting the method of search used for the review

Survival and recurrences

Five-year overall survival (OS) ranged from 64.8% to 97.6%. Three-year, 5-year, and 10-year weighted OS was 86.4%, 81.4%, and 73.6%, respectively [Table 3]. Distant recurrences were seen in 4%–30% 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*.[5] 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

Table 1: Clinical presentation pathological data from included studies

Authors	Period of study	*n*	Median age (years) (range)	Gender (male/female)	Symptoms (%)	Histological type (%)	Tumor size (mean) (range)	Central airway location (%)
Molina *et al*.	1972–2002	62	51 (6–78)	34/26 (1.3)	Cough (70) Dyspnea (51.7) Wheezing (38.3) Obstructive pneumonia (30) Hemoptysis (28.3) Fever (16.7)	ACC (64.5), MEC (32.3)	2.4	70.70
Zhu *et al*.	2001–2013	88	48 (7–75)	47/41 (1.1)	Cough (48.9) Dyspnea (9.1) Hemoptysis (20.5) Fever (15.9) Chest pain (5.7)	MEC (78.4), ACC (13.6), EMC (7.9)	2.5	15.90
Kang *et al*.	1995–009	48	41.5 (6–69)	31/17 (1.8)	NA	MEC (54.1), ACC (41.7), EMC (4.2)	3.4 (0.5–12 cm)	37.50
Pandey *et al*.	2012–2014	7	42.0 (27–52)	7/0	Hemoptysis (85.7) Dyspnea (85.7)	ACC (57.1), MEC (42.9)	3.5	100
ELnayal *et al*.	2001–2010	30	NA	13/17 (0.8)	NA	MEC (56.7), ACC (36.7), EMC (6.7)	2.7 (median) (0.8–11.4)	70

ACC: Adenoid cystic carcinoma, MEC: Mucoepidermoid carcinoma, EMC: Epithelial-myoepithelial carcinoma, NA: Not available

Table 2: Surgical data from studies included in the study

Authors	Management	Common surgical procedure (%)	Lymph node involvement (%)
Molina *et al*.	Surgery 71.3% Adjuvant RT 23.7%	Lobectomy (44.2) Tracheal resection (25.6) Pneumonectomy (18.6) Sleeve resection (9.3)	20
Zhu *et al*.	Surgery in 95.4% Adjuvant RT in 11.4% Adjuvant CT in 8%	Lobectomy (55.7) Sleeve lobectomy (18.2)	11.40
Kang *et al*.	Surgery primary modality in 48 (97.9%) Neoadjuvant treatment in 12.5% (*n*=6, CT in 5, chemoradiotherapy in 1) Adjuvant treatment in (*n*=19, RT in 12 and CT in 7)	Sleeve bilobectomy (31.2) Sleeve lobectomy (27.1) Tracheal resection (16.7) Pneumonectomy (14.6) Carinal sleeve resection (10.4)	19
Pandey *et al*.	Surgery alone 100%	Pneumonectomy (71.4) Lobectomy (14.2)	0
ELnayal *et al*.	NA	NA	NA

CT: Chemotherapy, RT: Radiotherapy, NA: Not available

Table 3: Survival and recurrence patterns in the included studies

Authors	Median follow-up (months) (range)	Recurrences (%)	Survival (%)
Molina *et al*.	NA	Local NA Distant 30.4	3-year OS=80 5-year survival=65 10-year survival=53
Zhu *et al*.	49 (3–134)	Local 4.5 Distant 12.5	3-year OS=91.3 5-year survival=86 10-year survival=80.6
Kang *et al*.	59.8 (0.7–155)	Distant 4.1	5 year OS=97.6 10 year OS=86.7
Pandey *et al*.	5 (1-30)	None	85.7 alive
ELnayal *et al*.	NA	30	3-year OS=84.7 5-year OS=64.8

OS: Overall survival, NA: Not available

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

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

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*.[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.[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*.[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*.[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*.[5] 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.[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.[3] 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*.[3] reported inferior 5- and 10-year OS rates due to larger number of cases with ACC (64.5%). Zhu *et al*.[4] and Kang *et al*.[5] reported slightly better OS as they had a larger share of cases with MEC.

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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