



# Pulmonary puzzles: salivary gland-type tumors of the lung and their metastatic equivalents

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**Summary** In the last decade, the understanding of lung neoplasms, particularly rare salivary gland-type tumors (SGT), has deepened significantly. This review intends to spotlight the latest findings, particularly emphasizing the differentiation between primary and metastatic SGTs in the lung.

**Keywords** Rare pulmonary tumors · Salivary gland-type · Review · Diagnosis pathway · Lung metastasis

## Abbreviations

<i>ACC</i>	Adenoid cystic carcinoma
<i>EMC</i>	Epithelial-myoepithelial carcinoma
<i>FISH</i>	Fluorescence <i>in situ</i> hybridization
<i>GAs</i>	Genetic alterations
<i>HCCC</i>	Hyalinizing clear cell carcinoma
<i>MEC</i>	Mucoepidermoid carcinoma
<i>MyC</i>	Myoepithelial carcinoma
<i>MyE</i>	Myoepithelioma
<i>NSCLC</i>	Non-small cell lung carcinoma
<i>PA</i>	Pleomorphic adenoma
<i>SGT</i>	Salivary gland tumors
<i>SqCC</i>	Squamous cell carcinoma

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*WES* Whole exome sequencing

## Introduction

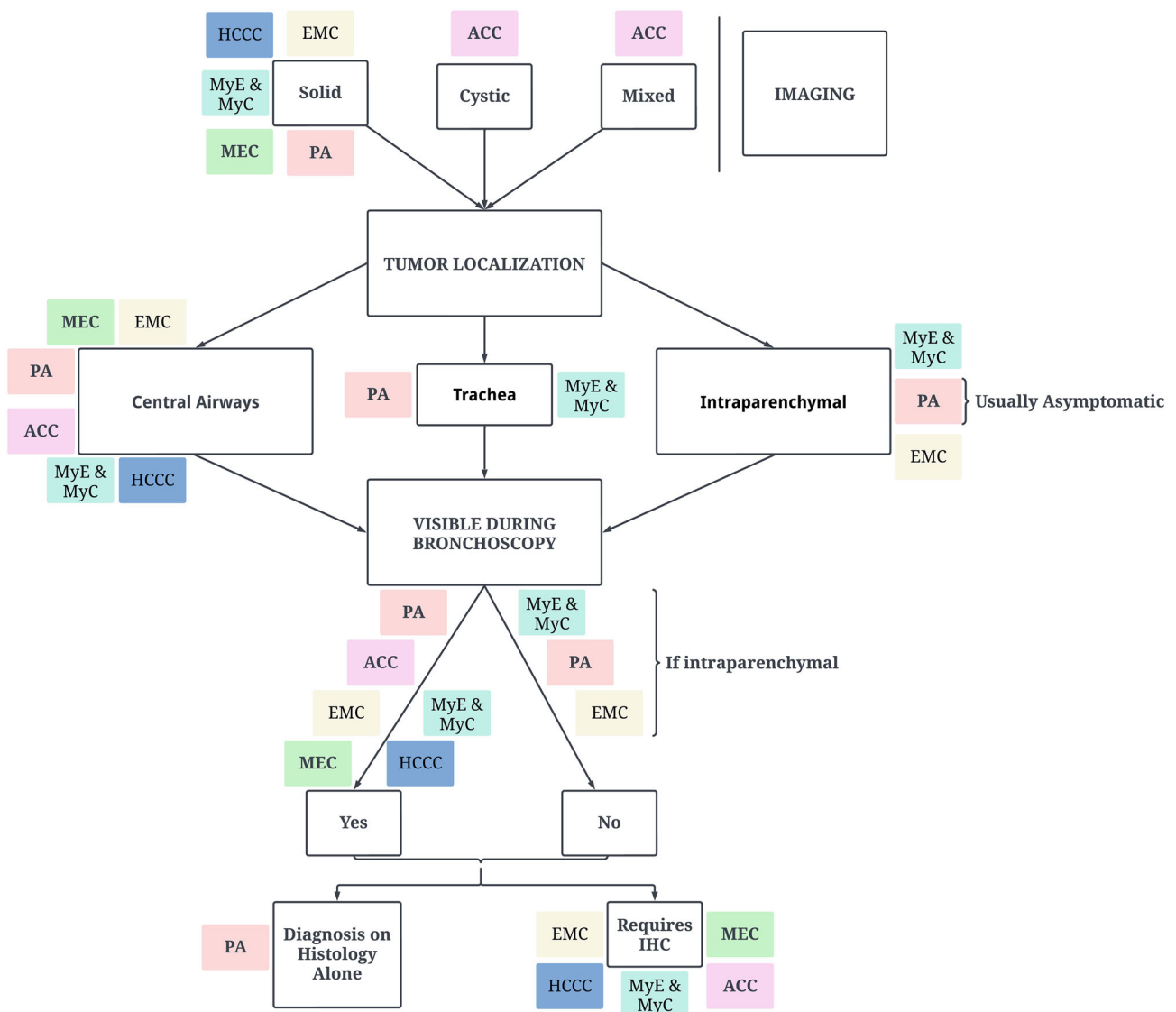
The realm of lung neoplasms is vast and varied, encompassing an array of histologic types. Among these, salivary gland-type tumors (SGT) stand out due to their rarity [1, 2]. Although they develop from minor salivary glands in the submucosa of the large airways [3], their occurrence rate is remarkably low, accounting for only 0.09–0.2% of all lung cancers [4, 5]. Their association with the tracheobronchial tree often results in patients presenting with symptoms such as cough, dyspnea, and hemoptysis due to obstruction.

A critical aspect that needs to be discerned is the differentiation of primary SGTs from metastatic tumors. Notably, metastatic SGTs have been predominantly recognized as originating from the head and neck, primarily, but occurrences from sites such as the breast, skin, and thymus have also been reported [1, 6–8]. Importantly, the lung is the primary site of metastasis in 63% of SGT [9].

In this short review, we will focus on characteristics of primary SGT of the lung and the possibility of their differentiation from metastatic SGT to the lung (Fig. 1).

## Lung salivary gland-type tumors

Based on the 2021 World Health Organization (WHO) classification, SGTs of the lung include pleomorphic adenoma (PA), adenoid cystic carcinoma (ACC), epithelial-myoepithelial carcinoma (EMC), mucoepidermoid carcinoma (MEC), hyalinizing clear cell carcinoma (HCCC), myoepithelioma (MyE), here focusing specifically on myoepithelial carcinoma (MyC; Fig. 2). Of note, while in the salivary glands in the head and neck region, the most common tumors are PA, the



**Fig. 1** Diagnostic flowchart for salivary gland tumors (SGT). PA pleomorphic adenoma, ACC adenoid cystic carcinoma, EMC epithelial–myoepithelial carcinoma, MEC mucoepider-

moid carcinoma, HCCC hyalinizing clear cell carcinoma, MyE myoepithelioma, MyC myoepithelial carcinoma, IHC immunohistochemistry

most common primary SGTs of the lung are MEC [1, 10]. Other types occur very sporadically.

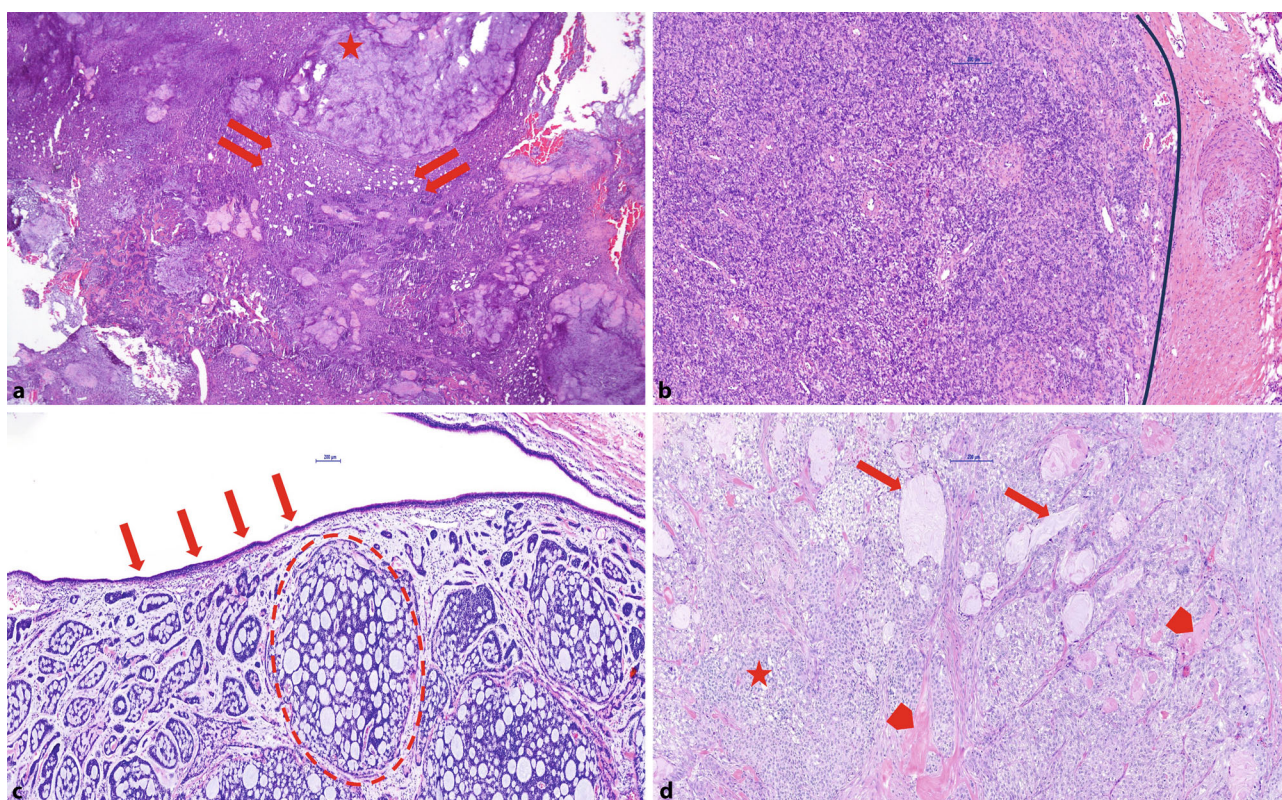
The prognosis of these tumors often hinges on their site of origin, in the lung, most of them are low-grade malignancies that grow slowly but have an invasive growth pattern. They occasionally recur and can present with metastases. ACC of the lung is known to be more aggressive, and it often presents at a more advanced clinical stage and is frequently deemed unresectable. In terms of age and demographics, SGT predominantly develops in adults during their 5th and 6th decades of life. However, there is an exception with MEC, which can also manifest in children, ranging from as young as 2 years to 78 years old. Overall, the gender distribution for these tumors is fairly even; only ACC shows a slight male predominance [9–12].

**From pathology to clinical perspective**

SGTs of the lung encompass a diverse range of morphology, each characterized by distinct molecular markers and clinical outcomes. Delving into these tumors’ histology, immunohistochemistry (IHC), molecular, and clinical intricacies provides a better understanding of their behavior and prognosis (Table 1).

**Mucoepidermoid carcinoma**

MEC, the most common SGT in the lung, is characterized by a mixture of mucous, intermediate, and squamoid cells [11–15]. Histologically, MEC of the lung is graded based on specific criteria that assess cellular morphology, mitotic activity, and the presence of necrosis. Low-grade MEC is characterized by well-differentiated cells, minimal mitotic activity,



**Fig. 2** **a** Pleomorphic adenoma: duct-like formations (acinar—red arrows) are noticeable within a cartilage-like (chondroid—red star) tissue matrix. **b** Myoepithelioma: tumor cells resembling epithelial cells, having round nuclei and a pinkish cytoplasm, are situated within hyalinized stroma; black line at the transition between the tumor and a fibrous capsule. **c** Adenoid cystic carcinoma: the tumor mainly consists of cribriform nests with well-defined round spaces filled with a lightly basophilic myxoid material (ground substance)—red dashed oval. Red arrows indicate respiratory epithelium, with emphasis on the location this tumor usually has—associated with an airway. **d** Mucoepidermoid carcinoma: abundant tumor glands filled with mucin (red arrows), situated within a thick fibrous tissue matrix (stroma—red arrowheads), the red star indicates hypercellular areas. The diagnosis is low-grade mucoepidermoid carcinoma

**Table 1** Salivary gland tumors (pleomorphic adenoma not included), main differential diagnosis, cell morphology for each salivary gland tumor and histological pattern, primary immunohistochemistry for diagnosis and molecular changes

SGT	Differential diagnosis	Cells/Patterns	Immunohistochemistry	Molecular changes
Mucoepidermoid carcinoma	Metastasis from head and neck salivary gland tumor— <i>clinical correlation is paramount</i>	3 cell types; cystic and solid growth pattern	P63, p40 in squamoid and intermediate cells	<i>MAML2</i> rearrangement, in 70–100%
Adenoid cystic carcinoma	Carcinoid tumors, basaloid SCC, and SCLC—IHC is usually enough for differential	Uniform, small cells; cribriform, solid, tubular, mixed	P63 focally, CD117 focally or diffusely	<i>MYB</i> rearrangement in 40%
Epithelial-myoepithelial carcinoma	IHC differentiation of the two components epithelial and myoepithelial is enough for diagnosis	Biphasic (cuboidal and spindle cells); tubular; trabecular, papillary, solid	Inner layer-panK, CK7, outer layer p63, p40, CK5/6, SMA, S100, ATF1	–
Myoepithelioma and myoepithelial carcinoma	Composed exclusively of myoepithelial cells—no ductal or tubular structures	Epithelioid, spindle, plasmacytoid cells, sometimes clear cytoplasm; solid and nested pattern	CK7, p63, p40, calponin, S100, SMA	<i>EWSR1</i> , <i>EWSR1-PBX1</i> , <i>EWSR1-ZNF444</i> , <i>FUS-KLF17</i>
Hyalinizing clear cell carcinoma	Low-grade MEC with clear cells, MyE, metastatic RCC or NSCLC	Cells with round to oval nuclei, clear to eosinophilic cytoplasm, hyalinizing acellular stroma	CK7, p63, p40, CK5/6	<i>EWSR1-ATF1</i> fusion, in 90%

RCC Renal cell carcinoma, NSCLC non-small cell lung cancer

and an absence of necrosis. The architecture typically includes cystic spaces lined by mucus-producing cells and a background of squamoid and intermediate cells. In contrast, high-grade MEC exhibits features such as marked cellular atypia, increased mitotic activity, and

the presence of necrosis. These tumors often show solid growth patterns with less cystic differentiation and a greater proportion of squamoid or intermediate cells [11, 12]. The presence of these features in MEC indicates a more aggressive behavior and correlates

with a lower survival rate, approximately 75%, compared to 95% in low-grade tumors [12]. Parenchymal invasion is also more commonly observed in high-grade tumors, occurring in about 50% of cases. Treatment recommendations for MEC hinge on the histological grade. For grade I (low-grade) tumors, surgical resection is the preferred approach. However, for more advanced grades (II and III, typically high-grade), adjuvant therapies, including radiotherapy or chemotherapy, are often considered to manage the increased risk of recurrence and metastasis [5]. HER2 expression has been documented in MEC of the salivary gland, particularly in those with high-grade features. However, in pulmonary MEC, HER2 staining has not been observed. In addition, common lung markers such as TTF-1 and Napsin A are typically negative in pulmonary MEC [11]. MEC is characterized by the fusion of the *CRTC1* and *MAML2* genes, present in up to 90% of those tumors. This genomic alteration aids in the diagnostic process, with fluorescence in situ hybridization (FISH) testing for the *CRTC1-MAML2* gene fusion serving as a reliable diagnostic tool [16, 17]. Differentiating MEC from adenosquamous carcinoma and squamous cell carcinoma (SqCC) can be challenging, especially in small biopsies. The clinical relevance of this distinction lies in the more favorable prognosis of low-grade MEC compared to high-grade variants and other non-small cell lung carcinoma (NSCLCs) [2]. Notably, the presence of the *CRTC1-MAML2* fusion is associated with better survival outcomes, while incomplete resection and nodal metastases are indicators of a poorer prognosis [18, 19].

### Adenoid cystic carcinoma

Pulmonary ACC, characterized by its biphasic morphology and cribriform, tubular, or solid patterns, presents a diagnostic challenge due to its morphologic overlap with other neoplasms. The differential diagnosis includes basaloid SqCC, carcinoid tumor, small-cell carcinoma, and PA. ACC of the lung typically exhibits positive IHC staining for several markers. These include cytokeratin 7, p63, p40, S100, calponin, and CD117. The expression pattern of p63 in ACC is particularly distinctive, manifesting as nuclear peripheral staining or, in cases with cribriform architecture, nuclear staining in the internal luminal cells [11]. Furthermore, CD117/c-KIT expression by IHC is present, providing additional aid in distinguishing ACC from other lung tumors [2]. Interestingly, mutations in the *KIT* gene are absent [13]. In head and neck ACC, *MYB* or *MYBL1* alterations are found at a higher frequency compared to their pulmonary counterparts. Specifically, 78% of head and neck ACC cases exhibit these genetic alterations. Within this subset, *MYB* alterations are present in 62% of cases, while *MYBL1* rearrangements are found in 16%. This contrast highlights a distinct molecular profile of head

and neck ACC compared to pulmonary ACC, where *MYB* or *MYBL1* rearrangements are observed in about 41% to 58% of cases [11, 20]. From a diagnostic perspective, testing for *MYB-NFIB* and *MYBL1-NFIB* gene fusions, using techniques like FISH or next generation sequencing, can be pivotal in confirming the diagnosis [14]. This is especially useful in small biopsies, where histologic presentation is not clear.

Clinically, ACC demonstrates an indolent course, but its propensity for perineural invasion and infiltrative growth limits the feasibility of complete resection. However, local recurrences, often multiple, can occur in a long follow-up, 10–15 years postresection. Factors such as the clinical stage at diagnosis, surgical margins, patient age, and growth pattern significantly determine prognosis [15].

Interestingly, in head and neck ACC, *NOTCH1* mutations, especially in the negative regulatory region and Pro-Glu-Ser-Thr-rich domains, mark a more aggressive subtype. These mutations are associated with solid tumor histology, advanced disease at diagnosis, higher metastasis rates, and shorter survival times. The efficacy of brontictuzumab against *NOTCH1*-mutant tumors suggests potential for targeted therapy in this subgroup of ACC [21]. This raises a significant question about the potential applicability of similar therapeutic strategies for lung ACC, particularly for cases exhibiting analogous molecular characteristics. This, however, remains unanswered, as there are no whole exome sequencing (WES) studies regarding lung ACC. The 5-year survival rates, favorable compared to other NSCLCs, underscore the importance of accurate diagnosis, and tailored clinical management. The distinction between primary ACC of the lung and metastatic ACC from salivary glands of the head and neck is very challenging. This difficulty arises because these two entities share the same morphologic, IHC, and molecular features. Therefore, differentiating between primary pulmonary ACC and metastatic salivary gland ACC based solely on histopathological and IHC analysis is not feasible. However, Hsu et al. reported that many solitary pulmonary ACCs, especially those present in the periphery of the lungs, are metastases from salivary glands [22]. This suggests that when encountering solitary pulmonary lesions, it is essential to consider and investigate extrathoracic primary sites, as these lesions might not be primary lung tumors but rather metastases from the salivary glands outside the lung [5].

### Epithelial–myoepithelial carcinoma

EMC of the lung, classified by the WHO as a low-grade salivary gland-type tumor, presents distinct histological subtypes as elucidated by Nakashima et al. in their 2018 case report and review of the literature [23]. The primary subtype, characterized by a dual ductal component of duct-forming epithelial and myoepithelial cells, is emblematic of EMC and suggests

a lower-grade tumor. This subtype is observed most frequently among EMC cases.

The second subtype, marked by a solid composition of spindle and polygonal-shaped myoepithelial cells, indicates a variation in cellular morphology within EMC. The third and most clinically pertinent subtype is myoepithelial anaplasia, characterized by increased nuclear atypia in myoepithelial cells, signifying a higher grade and more aggressive tumor behavior.

Immunohistochemically EMC demonstrates a biphasic pattern. The inner duct-forming epithelial cells are positive for cytokeratin 7, while the outer myoepithelial cells exhibit negativity for this marker. In contrast, the myoepithelial cells show positivity for S100 protein, SMA, p63, and cytokeratin 5/6. This IHC profile is critical in distinguishing EMC from other lung carcinomas and confirms the diagnosis. Despite the presence of myoepithelial anaplasia in some cases, EMC generally follows an indolent course. The differential diagnosis includes ACC and PA. The pathogenesis of EMC remains elusive. Most of these carcinomas are low-grade, with no recurrence observed after complete resection. However, there have been sporadic reports of metastasis to mediastinal lymph nodes. Certain factors, including a high mitotic count and nuclear pleomorphism, have been identified as adverse prognostic indicators [23, 24]. Regarding the molecular pathology of EMC, as detailed in the study by Urano et al. focusing on EMCs primarily in salivary glands of the head and neck, a high prevalence of *HRAS* mutations, particularly in codon 61, was found. In addition, *PIK3CA* and/or *AKT1* mutations were the second most frequent, often co-occurring with *HRAS* mutations. This molecular signature, especially the high frequency of *HRAS* mutations, was consistent across EMCs regardless of specific histological variations or the tumor's anatomic site, suggesting *HRAS* mutations as a common oncogenic event in EMC [25]. Unfortunately, molecular studies regarding EMCs of the lung are currently lacking.

### Myoepithelial carcinoma

Primary MyC of the lung is a rare tumor, originating from bronchial salivary gland-type tissue. Histologically, MyC exhibits diverse patterns, including solid, myxoid, reticular, and trabecular formations, often complicating its differentiation from other lung neoplasms. MyC typically shows positivity for cytokeratin, S100, calponin, and p63, aiding in its identification. Distinguishing benign from malignant forms relies on criteria such as cytologic atypia and mitotic activity. The rarity of PMC poses challenges in establishing definitive molecular characteristics; however, its diagnosis relies on a combination of histological and IHC findings. This tumor type's clinical behavior and prognosis remain poorly defined due to its scarcity. Genetic alterations, particularly *EWSR1* rear-

rangements, play a role in the diagnosis but are not exclusive to these tumors [26–29]. Myoepithelial tumors often exhibit *EWSR1* gene rearrangements, with a subset showing alternative *FUS* gene rearrangements [26, 27]. The presence of necrosis and a high mitotic count ( $\geq 5$  mitoses/2 mm<sup>2</sup>) are associated with a worse prognosis for these tumors [26–29].

### Hyalinizing clear cell carcinoma

HCCC, an extremely rare pulmonary SGT that is characterized histologically by atypical small-to-medium-sized epithelioid cells with light eosinophilic to clear cytoplasm. These cells exhibit round-to-oval nuclei and inconspicuous nucleoli, lacking significant pleomorphism and mitotic activity [2, 11]. The tumor cells are arranged in irregular nests, cords, tubular, and trabecular patterns, set within a loose myxoid stroma. Occasionally, these cells connect to the basal layer of the bronchial epithelium but lack keratinization and in situ carcinoma of the overlying epithelium. IHC, HCCC is positive for CK7, p40, CK5/6, and p63, and negative for PAX8, CD10, RCC, CAIX, TTF1, S100, CDX2, SATB2, CK20, calponin, HMB-45, Melan A, SOX10, WT-1, calretinin, D2-40, and SMA [29]. The initial diagnostic considerations for this tumor included low-grade mucoepidermoid carcinoma due to its clear cell features. The pathogenesis of HCCC is yet to be fully understood. However, the consistent presence of the *EWSR1-ATF1* fusion provides a diagnostic marker [31]. This genetic feature, combined with its unique morphologic and immunophenotypic profile, distinguishes HCCC from SqCC, MEC, and other lung tumors [2]. The consistent presence of the *EWSR1-ATF1* fusion provides a diagnostic marker [30]. They are low-grade tumors, clinically exhibiting an indolent course, with no reported recurrences after surgery, and no reported disease-related deaths [32].

### Treatment of advanced salivary gland-type tumors

The cornerstone of treatment for SGTs remains surgical resection aiming for complete resection with disease-free margins [33, 34]. Improved regional control is found with combined chemoradiotherapy, though without a corresponding survival benefit compared to radiotherapy alone. Systemic therapies are generally reserved for palliative care or in cases of rapid disease progression. However, the limited response and survival rates with conventional chemotherapy highlight the critical need for the identification of genetic alterations (GAs) that could guide the development of targeted therapies [35]. The exploration of targeted agents, such as those directed against *HER2*, is an emerging area in the treatment of these tumors. The discovery of *HER2* overexpression and amplification is promising for MEC and salivary duct carcinoma therapy. On the other hand, other tumor types, like

ACC, typically do not exhibit HER2 overexpression/amplification [11].

Our short review, while not specifically focusing on treatment outcomes, emphasizes the significance of detailed molecular characterization of SGTs not only for diagnosis but also for therapy decisions. It points toward a future of personalized medicine, where treatment strategies are tailored to the specific molecular characteristics of each tumor, potentially improving patient outcomes significantly.

## Conclusion

Primary pulmonary salivary gland-type tumors (SGTs) present a unique set of challenges in differential diagnosis and management. Understanding the intricate morphological, immunophenotypic, and molecular characteristics of these tumors is paramount for pathologists and clinicians. The rarity of these neoplasms necessitates a high index of suspicion and a thorough diagnostic approach, integrating clinical, radiological, and pathological data [2]. The favorable prognosis of most of these tumors, compared to other NSCLCs, highlights the importance of their recognition and accurate diagnosis for appropriate patient management. Continued research and detailed reporting of these rare entities are crucial for expanding our understanding and refining diagnostic criteria, ultimately improving patient outcomes.

## Take home message

Salivary gland-type tumors in the lung present a complex diagnostic challenge. Correlation of radiology, histology, immunohistochemistry, and molecular findings are needed for the right diagnosis. Differentiation between metastatic and primary tumors is needed for optimal therapy and patient care.

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### Further Reading

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