COMPREHENSIVE FIFTEEN-YEAR STUDY ON PRIMARY MALIGNANT SALIVARY GLAND TUMORS: DEMOGRAPHIC AND PATHOLOGICAL INSIGHTS

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COMPREHENSIVE FIFTEEN-YEAR STUDY ON PRIMARY MALIGNANT SALIVARY GLAND TUMORS: DEMOGRAPHIC AND PATHOLOGICAL INSIGHTS (Abstract): **Aim:** Primary epithelial malignant salivary gland tumors (MSGTs) constitute a rare and heterogeneous group of neoplasms, characterized by variable gender distribution, anatomical localization, and histopathological profiles. The national-level data on their epidemiology and histopathological characteristics are limited in Romania. This study aimed to evaluate primary epithelial MSGTs diagnosed over a 15-year period in our geographical area, in order to characterize their demographic and histopathological features. **Materials and Methods**: A retrospective analysis of 165 cases of primary epithelial MSGTs diagnosed in Sf. Spiridon County Hospital, Iasi, from 2010 to 2024, has been performed. **Results**: The cohort exhibited an equal gender distribution, with a men-to women ratio of 1:1.01 and a mean patient age of 60.56 ± 15.15 years. The majority of cases occurred in the seventh decade of life. At diagnosis, 61.21% of patients were smokers, 72.12% reported alcohol consumption, and 20% were classified as obese. The most common histological types were adenoid cystic carcinoma (26.06%), followed by mucoepidermoid carcinoma (18.78%) and salivary duct carcinoma (18.78%), while 46.65% of cases involved the parotid glands. A significant association between tumor location and patient's age ($p = 0.001$) or histological type and gender ($p < 0.001$) or between tumor location and histological type ($p = 0.014$) was registered, while there was no significant correlation between gender and age group ($p = 0.528$), or between tumor location and gender ($p = 0.574$), or histopathological type and patient's age groups ($p = 0.303$). **Conclusions:** A deeper insight into the demographic and pathological features of MSGTs could facilitate the design of new strategies of early detection and prevention of these malignancies. **Keywords:** PRYMARY EPITHELIAL MALIGNANT SALIVARY GLAND TUMORS, PAROTID GLAND; EPIDEMIOLOGY; HISTOPATHOLOGY.

INTRODUCTION

Malignant salivary gland tumors (MSGTs) are rare, comprising just approximately 2-6% of all head and neck cancers (1). MSGTs epidemiological profile has been continuously explored in recent decades in order to identify their general geographical distribution, their location and pathological profile, and the significant risk factors involved in their etiopathogeneses, providing a broader framework for the development of effective strategies for their prevention and treatment (2-4).

The crude and age-adjusted incidence

rates of MSGTs are estimated at 0.69 and 0.57 cases per 100,000 people per year, respectively, with 53,583 new cases registered worldwide in 2020 (3). Different epidemiological studies focused on this specific pathology revealed that MSGTs display the highest incidence in the European and North American population compared to other regions (5, 6). However, although their gender ratio varies across population in different reports (7), MSGTs have a female predominance, with a male-to-female ratio of 1:1.5 (8). Most cases affect the parotid glands, followed by the submandibular, sublingual, and minor salivary glands, being mainly registered in the sixth decade of life (9).

Advanced age, exposure to ionizing radiation, tobacco use, oncogenic viral infections, such as HPV and CMV, and low-fiber diet are well-established risk factors for MSGTs development (10).

Mucoepidermoid carcinoma, adenoid cystic carcinoma, carcinoma ex-pleomorphic adenoma, and adenocarcinoma are the most prevalent histological types of salivary gland cancers, each displaying a particular epidemiological profile (11).

Limited data on the MSGTs incidence in Romanian population are available in literature, mostly related to their lower incidence and the implementation stage of regional data collection for salivary glands tumors in the National Cancer Registry in our country (12). Furthermore, the population-based epidemiological studies reporting histology-specific incidence rates in MSGTs, including in Romanian population, are still limited due to their rarity and heterogeneity. In this context, our study aims to analyze the epidemiological pattern of primary epithelial MSGTs incidence in our geographical area.

MATERIALS AND METHODS

Our retrospective analysis was performed in the Department of Pathology of "Sf. Spiridon" County Hospital, Iasi. The records of 300 cases of MSGT cases selected from the hospital database, over 15 years (January 1st, 2010 to December 31th, 2024) were analyzed for the demographical and histopathological characteristics (12). The eligibility criteria included the confirmed histopathological diagnosis of primary epithelial MSGTs and accurate demographical information. The exclusion criteria were the following: uncertain pathologic diagnosis, benign type of salivary gland tumors, non-epithelial MSGTs, secondary epithelial MSGTs, or lack of complete patient' information. Following the application of these exclusion criteria, 165 cases of primary epithelial MSGTs were eligible for analysis (12). All cases have been histopathologically re-evaluated and reclassified according to the latest WHO Classification (10).

Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY, USA) and Microsoft Excel 2016. Descriptive statistical parameters were calculated, encompassing frequencies, percentages, means, and standard deviations. Pearson chi-square test has been applied to evaluate the correlations between different variables and a p value < 0.05 was considered as statistically significant. The strength of significant associations was evaluated by Cramer's V (V), using standard interpretation criteria (weak = 0.10, moderate = 0.30, and strong > 0.50).

This research was approved by the Research Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy Iasi (approval no. 500/30.11.2024) and Ethics Committee of "Sf. Spiridon" County Hospital Iasi (approval no. 99/8 No-

vember 2024), in alignment with the Declaration of Helsinki's principles regarding medical research involving human participants.

RESULTS

Clinical and epidemiological distribution

Our study included 165 cases of primary epithelial MSGTs, with a relatively equal gender distribution, 83 men (50.3%) and 82 women (49.7%), with a men-to-women ratio of 1:1.01. The mean patients' age group was 60.56 ± 15.15 years, displaying relatively similar gender ranges, with 60.99 ± 15.70 years in women and 60.16 ± 14.67 years in men. The oldest patient included in our cohort was 87 years old, while the youngest was 17 years old. Most of cases were registered in 60-69 age group, with 29.7% of cases, followed by 70-79 age group, with 24.2% of cases, and 50-59 age group, with 15.2% of cases (Fig. 1).

Regarding the gender distribution according to age groups, 22 patients (13.33%) were included in 60-69 age group and the same amount in 70-79 age group, with only 3 patients (1.81%) included in 20-29 age group, in women. Most men were included in 60-69 age group (27 cases; 16.36%) and 70-99 age group (18 of cases; 10.90%) (Fig. 2). The statistical analyses revealed no significant association between patients' gender and their age groups (p = 0.528; effect size: V = 0.267).

Most patients were smokers (n = 101; 61.21%), including current smokers (n = 53; 32.12%) and former smokers (n = 48; 29.09 %). Regarding the alcohol consumption, 46 patients (27.88%) were non-drinkers and 119 patients (72.12%) reported alcohol consumption. At the time of diagnosis, 33 patients (20.0%) were obese, 62 patients (37.57%) were overweight, and the remaining patients had a normal weight.

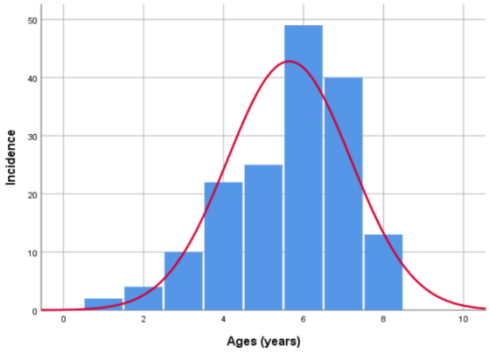

Fig. 1. Primary malignant epithelial salivary gland tumors distribution by age

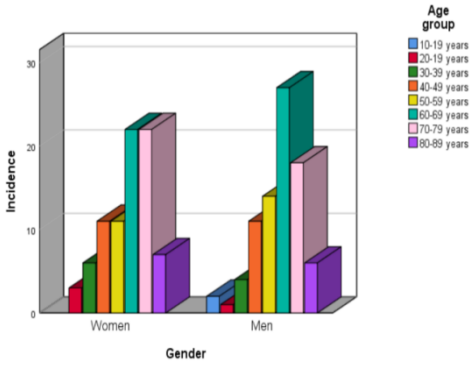

Fig. 2. Primary malignant epithelial salivary gland tumors distribution by gender and age group

Tumor location. The parotid glands represented the most frequent tumor location, accounting together 46.65% of all cases included in our research, followed by the palatine glands, with 22.42% of cases, and the submandibular glands, with 13.33% of cases. Tumors involving the sublingual, labial, and lingual glands were extremely rare. Analysis of MSGTs distribution according to age group and anatomical loca-

tion showed more cases of parotid tumors across all age groups. Data analysis revealed a significant association between primary epithelial MSGTs location and patient's age (p = 0.001, V = 0.613), whereas no statistically significant association was found between tumor location and gender (p = 0.574; V = 0.252).

Tumor Histopathological Features. On gross examination, primary epithelial MSGTs appeared as white to tan-grey tumor masses with ill-defined or infiltrative margins and firm consistency, occasionally associated with areas of necrosis. Tumor size ranged from 7 to 104 mm in diameter, with a mean size of 36.61 $\pm$ 17.97 mm.

The most frequent histopathological types identified in our study was adenoid cystic carcinoma (n = 43; 26.06%), followed by mucoepidermoid carcinoma and salivary duct carcinoma (n = 31; 18.78% each) (Figs. 3-5). Other primary epithelial MSGTs, such as acinic cell carcinoma, adenocarcinoma not otherwise specified, and squamous cell carcinoma were less frequently diagnosed than the previous tumor types (Table 1) (Fig. 6). Only 3 cases (1.82%) of epithelial-myoepithelial carcinoma were identified in our study group.

TABLE I.

Primary epithelial MSGTs distribution by gender and histopathological diagnosis in the study group

	AdCC	MEC	SDC	AcCC	AC NOS	CXPA	EMC	SCC	Total
Women	28 (16.97%)	10 (6.06%)	5 (3.03%)	18 (10.90%)	15 (9.09%)	3 (1.82%)	1 (0.60%)	2 (1.21%)	82 (49.69%)
Men	15 (9.09%)	21 (12.72%)	26 (15.75%)	6 (3.64%)	8 (4.84%)	2 (1.21%)	2 (1.21%)	3 (1.82%)	83 (50.30%)
Total	43 (26.06%)	31 (18.78%)	31 (18.78%)	24 (14.54%)	23 (13.93%)	5 (3.03%)	3 (1.82%)	5 (3.03%)	165 (100%)

AdCC - adenoid cystic carcinoma; AcCC - acinic cell carcinoma; AC NOS - adenocarcinoma, not otherwise specified; CXPA - carcinoma ex pleomorphic adenoma; EMC - epithelial-myoepithelial carcinoma; MEC - mucoepidermoid carcinoma; SCC - squamous cell carcinoma; SDC - salivary duct carcinoma.

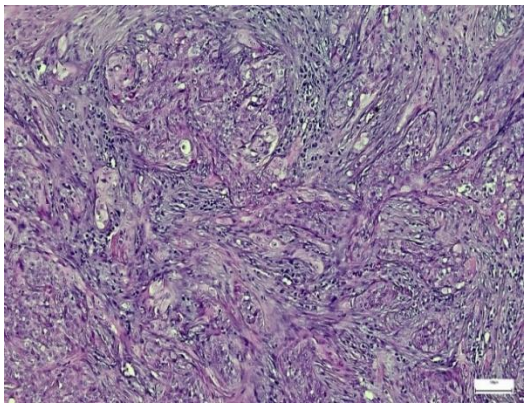

Fig. 3. Salivary gland adenoid cystic carcinoma, H&E staining, 4x

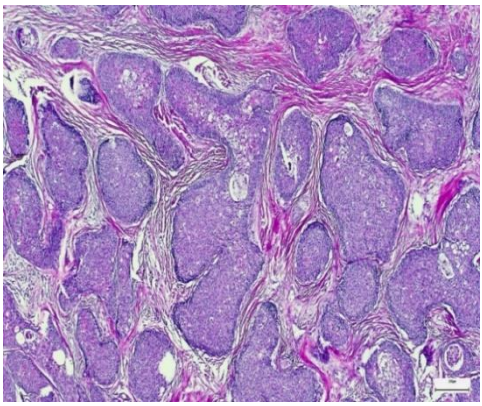

Fig. 4. General view of a salivary gland mucoepidermoid carcinoma, H&E staining, 4x

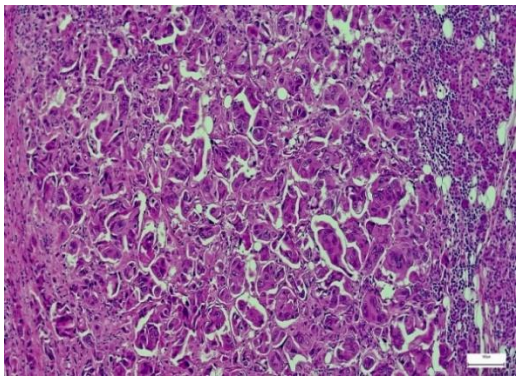

Fig. 5. Tumor-associated lymphocytic infiltrate in a salivary duct carcinoma, H&E staining, 10x

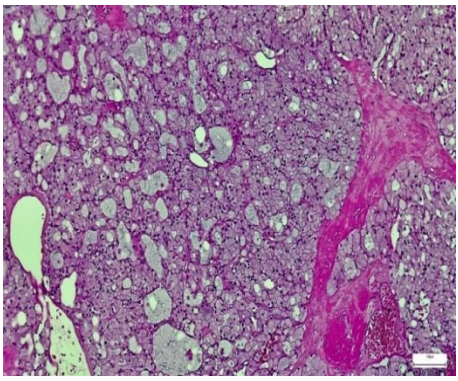

Fig. 6. Finely vacuolated cytoplasm and round nuclei in acinic cell carcinoma, H&E staining, 4x

The histological distribution of primary epithelial MSGTs revealed a predominance of adenoid cystic carcinoma among women compared to men (28 cases, 16.97% vs. 15 cases, 9.09 %). A similar gender distribution was also observed in acinic cell carcinoma and adenocarcinoma not otherwise specified (Table 1). In contrast, salivary duct carcinoma, with 31 cases (18.78%), showed a male gender propensity, with 26 cases in men vs. five cases in women.

Statistical analysis demonstrated a significant association between gender and tumor histological type, with a moderate effect size ($p < 0.001$, V = 0.438).

Adenoid cystic carcinoma was the most common salivary gland malignancy across all age groups, with a peak occurrence in patients aged between 60 and 79 years. Mucoepidermoid carcinoma was most frequently diagnosed in the eighth decade of life, with 8 cases (4.84%), while salivary duct carcinoma was identified in the seventh decade of life (13 cases; 7.87%). Only two cases were registered in patients under 20 years, being diagnosed as adenoid cystic carcinoma and salivary duct carcinoma, each type in a case. The statistical analysis revealed no association between the histopathological type and the patients' age groups ($p = 0.303$, V = 0.229).

Moreover, mucoepidermoid carcinoma was the most frequent histological type, involving the parotid gland in 15 patients (9.09%). Adenoid cystic carcinoma was predominantly located in the palatine glands (n = 14 cases; 8.48%), followed by the parotid gland (n = 13 cases; 7.87%). Epithelial-myoepithelial carcinoma affected the parotid and buccal glands (1.21% and 0.60%, respectively), while squamous cell carcinoma involved the parotid and submandibular glands (1.82% and 1.21%, respectively). The statistical analysis showed a significant association between the histological type of primary epithelial MGSTs and tumor location ($p = 0.014$; effect size V= 0.313).

DISCUSSION

The salivary gland cancer development is supported by a complex environmental and genetic interaction. Thus, obesity, autoimmune disorders, chemical exposure, ionizing radiation, alcohol drinking, increased oxidative stress and viral infections, including Epstein-Barr virus (EBV), human herpesvirus-8 (HHV-8), cytomegal-

ovirus (CMV), have been incriminated in the etiopathogeny of different malignancies, including in that of salivary glands tumors (4, 13-15). More recently, the chronic inflammation related to chronic hepatitis C (16) has been also related to an increased risk for the development of salivary gland malignancies (17). However, future research may evaluate the impact of these different factors on salivary gland parenchyma, along with the molecular profile associated to salivary gland oncogenesis.

Epidemiological studies consistently show that MSGTs predominantly affect older patients (18, 19), particularly those aged 60-79 years (1). In this context, a recent study reported a mean age of 63.38 years (range, 21-97 years) (18), while another study registered a mean age of 68 years (range 15−105 years) (19) among MSGT patients, rates which are comparable to the mean age of 60.56 ± 15.15 years (range 17- 87) years registered in our research. All these results support the observation that salivary gland cancers are more prevalent in older persons, likely due to the progressive accumulation of genetic mutations, age-related decline in DNA repair mechanisms, and chronic exposure to environmental risk factors.

MSGTs account for approximately 21.7% of all salivary gland tumors (20), most commonly involving the parotid gland, followed by the submandibular, sublingual, and minor salivary glands (9, 18, 21). All these data partially align with our findings, in which parotid gland involvement was predominant, followed by the palatine glands and the submandibular glands, while minor salivary glands were rarely affected. Our results are also consistent with another study reporting the parotid gland as the most frequently involved location (31 cases), followed by the submandibular gland (10 cases) and minor salivary glands (8 cases) (4). Furthermore, a recent large-scale analysis of 10,808 cases of primary major salivary gland carcinoma demonstrated that tumors were most commonly located in the parotid gland, followed by the submandibular and sublingual glands (19). The variability of the reported data is most likely attributable to differences in sample size, study design, and the period of time evaluated. These factors may also explain the variability in gender distribution reported across studies on MSGTs, with some showing a predominance in women (53.1%) (4), others in men (55.6%) (18), and others a near-equal distribution between genders (22), as observed in our study.

Adenoid cystic carcinoma and mucoepidermoid carcinoma were the most frequent histopathological types of MSGTs identified in our study, a feature consistent with previous reports (1, 4, 23). However, a notable number of cases were diagnosed as salivary duct carcinomas (18.78%), which may represent a distinctive feature of our cohort. This finding is in contrast with other studies reporting acinic cell carcinoma (24) or squamous cell carcinoma (4) among the three most common MSGTs histological types. These differences may be attributed to cohort size, demographic characteristics, and advances in diagnostic classification, particularly in relation to salivary duct carcinoma diagnosis in our geographical area.

The most common location for mucoepidermoid carcinoma in our study was the parotid gland (9.09%), which align with the findings of Kızıl et al. but in disagreement with another study which found minor glands as the most common site (1, 25). Additionally, mucoepidermoid carcinoma

was mainly diagnosed in the eighth decade of life in our study, in contrast with other studies reporting a peak incidence in the fifth (26) or sixth decades (27). This discrepancy may be attributed to genetic particularities of our population, cumulative exposure to different risk factors, and cohort selection bias.

In comparison with mucoepidermoid carcinoma, adenoid cystic carcinoma was the most frequent malignancy across all age groups, with a peak incidence between 60 and 79 years and a slightly higher incidence in women, findings that are consistent with other reports (28-30). It also accounts for approximately 10% of all tumors of the major salivary glands and 30% of tumors of the minor salivary glands (31). These data agree with our observations, with 8.48% adenoid cystic carcinoma cases occurring in the palatine glands and 7.87% in the parotid gland.

Salivary duct carcinoma is a rare primary epithelial MSGT, characterized by a male predominance, a high incidence in the seventh and eighth decades of life, whereas squamous cell carcinoma mainly involves the parotid and submandibular glands (28, 32, 33). Similar data were observed in our study, with most salivary duct carcinoma cases occurring in older men, in the seventh decade of life, with only a case diagnosed in a patient under 20 years of age, while squamous cell carcinoma predominantly affected the parotid and submandibular glands (1.82% and 1.21%, respectively) (34). The different localization of MSGTs may be attributed to the histological and molecular heterogeneity of these glands, as well as to variations in size, function, and exposure to oncogenic factors, which influence their specific susceptibility to malignant transformation.

Taken together, MSGTs represent a relatively rare group of neoplasms, characterized by variable gender distribution, histopathological profiles, and anatomical distribution across the salivary glands, predominantly affecting older individuals. Understanding the epidemiological landscape, potential risk factors, and pathological characteristics of these malignancies is crucial for early diagnosis, which may ultimately improve patients' prognosis.

CONCLUSIONS

This retrospective study provides valuable insights into the characteristics and behavior of primary epithelial MSGTs within our geographical region. Conducted over an extended period of time, this research provides a significant perspective on the epidemiological and pathological features of these rare malignancies in North-East Romania.

CONFLICT OF INTERESTS AND FUNDING

The authors declare that there is no conflict of interests, and they received no specific funding regarding this scientific research.

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