

Clinicopathological analysis of salivary gland tumors over a 15-year period

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Abstract: Salivary gland tumors (SGT) are rare neoplasms that generate interest due to their histopathological diversity and clinical behavior. The aims of the present study were to investigate clinicopathological aspects of SGTs diagnosed at a tertiary health center and compare the findings with epidemiological data from different geographic locations. Cases of tumor in the head and neck region at a single health center in the period between 1995 and 2010 were reviewed. Patient gender, age and ethnic group as well as anatomic location, histological type and clinical behavior of the tumor were recorded. Availability of complete information about these aspects was considered the inclusion criteria. Descriptive statistical analysis of the data was performed using the frequencies of categorical variables. Among the 2168 cases of tumors in the head and neck region, 243 (11.20%) cases were diagnosed in the salivary glands, 109 of which met the inclusion criteria: 85 (78%) benign tumors and 24 (22%) malignant tumors. Mean patient age was 46.47 years. The female gender accounted for 56 cases (51.4%) and the male gender accounted for 53 (48.3%). The major salivary glands were affected more (75.2%) than the minor glands. The most frequent benign and malignant SGTs were pleomorphic adenoma (81.2%) and adenoid cystic carcinoma (58.3%), respectively. In conclusion, pleomorphic adenoma and adenoid cystic carcinoma are the most frequent benign and malignant lesions, respectively. Comparing the present data with previous studies on SGTs, one may infer that some demographic characteristics and the predominance of malignant tumors vary in different geographic regions.

Keywords: Neoplasms; Salivary Glands; Adenoma, Pleomorphic; Carcinoma, Adenoid Cystic; Carcinoma, Mucoepidermoid.

Introduction

Salivary glands tumors (SGTs) are uncommon neoplasms that pose a diagnostic challenge due to their complex histopathological features.¹ Moreover, SGTs exhibit considerable variation with regard to clinical aspects, biology and clinical behavior.^{2,3,4}

SGTs represent 3 to 6% of all tumors of the head and neck region, with an annual incidence throughout the world ranging from 0.05 to 2 cases per 100,000 individuals.⁵ Epidemiological data reveal different frequencies of SGTs in distinct ethnic groups and geographic locations, which makes it difficult to establish global estimates.^{1,6,7,8,9,10,11,12,13,14,15,16} Although



studies provide valuable knowledge, some data are contradictory. Local records are a useful strategy for the analysis of the distribution and particular features of SGTs in a specific population and the establishment of appropriate treatment.

The aims of present study were to describe demographic and clinicopathological aspects of SGTs diagnosed at a tertiary health center and compare the findings with epidemiological data from different geographic locations.

Methodology

A retrospective analysis was carried out using archival data from the pathology laboratory of a tertiary health center located in southern Brazil *Hospital de Clínicas de Porto Alegre*. This study received approval from the Institutional Ethics Committee (protocol no. 130152/12).

In a 15-year period spanning from 1995 to 2010, 2168 cases of tumors in the head and neck region were identified, 243 of which were SGTs. Clinical data regarding age, gender, clinical aspects, tumor localization, TNM Classification, treatment and follow-up information (clinical outcome and survival time) were retrieved from medical files. The follow-up period was defined as the time from diagnosis until the last visit to the hospital. Availability of complete information about these aspects was considered the inclusion criteria and based on these only 109 were included. Slides stained with hematoxylin-eosin of all cases were reviewed based on the Histologic Typing of Salivary Gland Tumors established by the World Health Organization (WHO).¹⁷ Continuous variables were expressed as mean, median and standard deviation values. Categorical variables were expressed as absolute number of cases and percentage values.

Results

Among the 109 cases of SGTs, 81 (74.3%) tumors were located in major salivary glands and 28 (25.7%) were located in minor salivary glands. The most frequent location among the major salivary glands was the parotid gland (66.9%), followed by the submandibular gland (7.3%). Among the minor glands, the most frequent location was the palate

(14.6%). No cases occurred in the sublingual gland (Figure and Table 1).

The male gender accounted for 53 cases (48.3%) and the female gender accounted for 56 (51.4%): male-to-female ratio of 0.9:1 for benign tumors and 1:1 for malignant tumors (Table 2). The majority of the tumors occurred in patients aged 41 to 60 years (median: 45 years). Mean patient age was 46.47 years (47.6 years for benign tumors and 42.3 years for malignant tumors). Young individuals (0-20 years-old) were the second group more affected by malignant tumors (25%) (Table 3).

Eighty-five cases (78%) were classified as benign tumors and 24 (22%) were malignant tumors (benign-to-malignant ratio of 3.5:1). The proportions differed depending on the type of salivary gland analyzed. Among the 81 cases of SGT in the major glands, 67 (82.7%) were benign and 14 (17.3%) were malignant. Among the 28 cases in minor salivary glands, 18 (64.3%) were benign and 10 (35.7%) were malignant (Table 1). Among the 85 benign tumors, 68 (79.06%) were pleomorphic adenoma and 16 (18.6%) were cases of Warthin's tumor. Among the 24 malignant tumors, 14 (58.3%) were adenoid cystic carcinoma, five (20.8%) were mucoepidermoid carcinoma and five (20.8%) were acinic cell carcinoma (Table 1).

Adenoid cystic carcinoma and mucoepidermoid carcinoma were classified based on the WHO Histologic Typing of Salivary Gland Tumors.¹⁷ Among the 14 cases of adenoid cystic carcinoma,

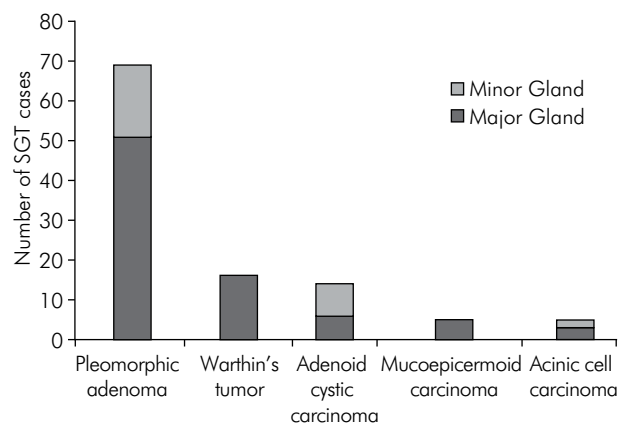


Figure. Distribution of 109 salivary gland tumors according to occurrence in major or minor salivary glands.

Table 1. Distribution of 109 salivary gland tumors according to anatomic location.

	Parotid		Submandibular		Palate		Other	
	n	%	n	%	n	%	n	%
Benign tumors								
Pleomorphic adenoma	48	69.6	3	4.3	11	15.9	7	10.1
Warthin's tumor	16	100.0	0	0.0	0	0.0	0	0.0
Subtotal (% in the group of benign tumors)	64	75.3	3	3.5	11	12.9	7	8.2
Malignant tumors								
Adenoid cystic carcinoma	3	21.4	3	21.4	4	28.6	4	28.6
Mucoepidermoid carcinoma	3	60.0	2	40.0	0	0.0	0	0.0
Acinic cell carcinoma	3	60.0	0	0.0	1	20.0	1	20.0
Subtotal (% in the group of malignant tumors)	9	37.5	5	20.8	5	20.8	5	20.8
Total (% according n = 109)	73	66.9	8	7.3	16	14.7	12	11.0

Table 2. Histologic and gender distribution of 109 salivary gland tumors.

	n = 109	%	% in the group of benign or malignant tumors	Gender			
				Male		Female	
				n	%	n	%
Benign tumors							
Pleomorphic adenoma	69	63.3	81.2	31	28.4	38	34.9
Warthin's tumor	16	14.7	18.8	10	9.2	6	5.5
Total	85	78	100	41	37.6	44	40.4
Malignant tumors							
Adenoid cystic carcinoma	14	12.8	58.3	6	5.5	8	7.3
Mucoepidermoid carcinoma	5	4.6	20.8	3	2.7	2	1.8
Acinic cell carcinoma	5	4.6	20.8	3	2.7	2	1.8
Total	24	22	100	12	10.9	12	10.9

Table 3. Distribution of 109 benign and malignant salivary gland tumors according to age (in years).

	0-20		21-40		41-60		> 61	
	n	%	n	%	n	%	n	%
Benign tumors								
Pleomorphic adenoma	5	7.2	24	34.8	28	40.6	12	17.4
Warthin's tumor	0	0.0	0	0.0	9	56.3	7	43.8
Subtotal (% in the group of benign tumors)	5	5.9	24	28.2	37	43.5	19	22.4
Malignant tumors								
Adenoid cystic carcinoma	1	7.1	2	14.3	8	57.1	3	21.4
Mucoepidermoid carcinoma	2	40.0	0	0.0	2	40.0	1	20.0
Acinic cell carcinoma	3	60.0	2	40.0	0	0.0	0	0.0
Subtotal (% in the group of malignant tumors)	6	25.0	4	16.7	10	41.7	4	16.7
Total (% according n = 109)	11	10.1	28	25.7	47	43.1	23	21.1

seven (50.0%) cases were cribriform, five (35.7%) were tubular and two (14.3%) were solid. Among the five cases of mucoepidermoid carcinoma, four were classified as low-grade and one was classified as intermediate-grade.

Regarding the clinical aspects, all benign tumors were nodules, whereas malignant tumors were nodules in 19 cases (11 cases of adenoid cystic carcinoma, four cases of mucoepidermoid carcinoma and four cases of acinic cell carcinoma) and ulcerated nodules in five cases (three cases of adenoid cystic carcinoma, one case of mucoepidermoid carcinoma and one case of acinic cell carcinoma). Among the 24 malignant tumors, 11 (45.8%) cases were classified as TNM stage I or II and 13 (54.2%) cases were classified as stage III or IV.

All patients underwent surgical treatment. Thirteen patients (11.92%) with malignant tumors also underwent radiation therapy. Among these patients, seven (53.8%) cases were adenoid cystic carcinoma, three (23.1%) were mucoepidermoid carcinoma and three (23.1%) were acinic cell carcinoma. The follow-up period ranged from four to 17 years (mean: 7.4 years). During the follow-up period, 19 patients (79.2%) of malignant lesions remained alive without recurrence and only one (4.2%) remained alive but with recurrence (adenoid cystic carcinoma). One patient (4.2%) died due to an unspecified cause and three (12.6%) died due to the tumor (TNM stages III and IV): one case (4.2%) of acinic cell carcinoma and two cases (8.4%) of adenoid cystic carcinoma. Recurrence was observed in four cases (3.66%) of pleomorphic adenoma and four cases (3.66%) of adenoid cystic carcinoma.

Discussion

A morphologically diverse group of rare tumors arises from salivary glands. These tumors have different biological behaviors and their etiopathogenesis remains unknown.^{2,5} Epidemiologic studies conducted in different parts of the world report differences in the incidence as well as frequency of histological types of SGTs (Table 4). The present study reviewed the demographic and clinicopathologic aspects of 109 cases of SGTs diagnosed at a tertiary health center and the findings are in general agreement with data reported in previous studies.^{1,8,10,12,15,16,18}

According to the literature, the most common clinical presentation of SGT is a well-circumscribed nodular tumor with a normal overlying surface color. SGTs are usually asymptomatic and affect females more, with peak incidence occurring the fifth and seventh decades of life.^{10,15,17,19,20,21,22} The clinical features that allow the differentiation of benign and malignant SGTs are the evolutionary course, pain and ulceration. Benign tumors tend to be insidious and slow growing, with an average course of three to six years and no adherence to surrounding tissues. Malignant lesions exhibit fast growth (often less than one year of evolution) and adhere to deep layers, with an ulcerated or telangiectatic surface. Pain is the most suggestive characteristic of malignancy.¹⁷ In the present series, the majority of clinical characteristics observed were similar to those reported in previous studies. Patient age ranged from nine to 81 years old, with a mean of 46.47 years. The tumors were all nodules and 4.6% were ulcerated. The only difference in comparison to previous reports was the similar male-to-female ratio (0.94:1) with both benign and malignant tumors. Although uncommon, Lukšić *et al.*¹⁵ and Tian *et al.*¹⁶ report similar findings.

Major salivary glands were affected more than minor glands, especially the parotid gland (66.9%), followed by palatine glands (14.7%). Similar results are described in the majority of studies on SGTs (Table 4), including those from Brazil (Table 5).^{1,6,7} The predominance of SGTs in major salivary glands may be explained by the fact that the present study was conducted at tertiary health center that receives most patients with parotid tumors. SGTs in minor salivary glands are usually diagnosed and treated at primary and secondary services, whereas only malignant SGTs in major salivary glands are referred to the hospital service.

Benign SGTs predominated in the major glands and comprised 78% of all salivary tumors, which is similar to rates reported in studies conducted in Iran,¹⁹ Congo,¹⁸ the United Kingdom,²³ Jordan,²⁴ Brazil^{6,7} and China,¹⁶ in which benign tumors accounted for more than 50% of all salivary tumors, suggesting that such tumors are the predominant form of SGTs worldwide. In the present study, the benign-to-malignant ratio was 3.5:1. Few studies report a greater prevalence

Table 4. Distribution of salivary gland tumors in different countries.

Region	Authors	Number of cases (n)	Benign	Malignant	Major Minor PA CAC MEC				
					(% of all tumors)				
China	Tian <i>et al.</i> 2010	6982	67.9	32.1	71.6	28.4	47	9.7	9.6
China	Li <i>et al.</i> 2008	3461	59.8	40.2	73.6	26.4	51.3	7.3	7.5
USA	Spiro <i>et al.</i> 1986	2807	54.5	45.5	78	22	45.4	10	15.7
Finland and Israel	Bello <i>et al.</i> 2012	1888	85.1	14.9	90	10	50	3.5	3.2
Croatia	Luksic <i>et al.</i> 2011	779	64.2	35.8	72.8	27.2	47.2	11.7	8.2
UK	Jones <i>et al.</i> 2008	741	64.9	35.1	38.6	61.4	44.4	8.4	11.5
Brazil	de Oliveira <i>et al.</i> 2009	599	78.3	21.7	78.3	21.7	67.8	6.5	4.8
Brazil	Ito <i>et al.</i> 2009	496	67.5	32.5	77.2	22.8	54.2	7.9	13.5
Brazil	Fonseca <i>et al.</i> 2012	493	50.5	49.1	74.8	25.1	85	17.7	31.4
Italy	Ascani <i>et al.</i> 2006	454	89.2	10.3	93.4	6.6	63.2	1.8	3.3
Nigeria	Lawal <i>et al.</i> 2013	413	46.5	53.5	55	45	40.9	22.5	14.8
Mexico	Meija-Velazquez <i>et al.</i> 2012	360	67	23	76.4	23.6	65.6	5	4.7
Israel	Bello <i>et al.</i> 2012	330	66.4	33.7	66.7	33.3	70.5	31.8	28.2
Congo	Kayeme <i>et al.</i> 2002	275	65.5	34.5	61.5	38.5	55.3	16	8
Uganda	Vuhahula 2004	268	32.8	67.2	54.1	45.9	73.8	29.3	20.3
Jordan	Ma'aitha <i>et al.</i> 1999	221	68.3	31.7	81	19	62.9	5.4	17.2
Tanzania	Masanja <i>et al.</i> 2003	133	54	46	42.4	57.6	44.4	24.8	9.8
Iran	Ansari <i>et al.</i> 2007	130	68.5	31.5	86.1	13.9	65.4	2.3	11.5
Brazil	Present study	109	78	22	74.3	25.7	63.3	12.8	4.6
Nigeria	Otoh <i>et al.</i> 2005	79	55.7	44.3	58.2	41.8	44.3	8.9	10.1

Table 5. Reports of salivary gland tumors in different states and regions in Brazil.

State/Region	Authors	Number of cases (n)
Goiás/Middle-West	de Oliveira <i>et al.</i> 2009	599
Paraná/South	Ito <i>et al.</i> 2009	496
Paraná/South – São Paulo/Southeast	Fonseca <i>et al.</i> 2012	493
Rio Grande do Sul/South	Present study	109

of malignant SGTs.¹¹ In such cases, the uncommon findings may be explained by the fact that the studies were conducted at tertiary centers, which receive more severe cases of SGTs.

Pleomorphic adenoma is a benign neoplasm composed of epithelial and myoepithelial cells arranged in a large variety of morphological patterns, with areas of mesenchymal differentiation. In the present series, this tumor was the most frequent type of SGT, accounting for 63.3% of all tumors and 81.2% of benign tumors. The majority of such cases (73.9%) were located in major salivary glands. The frequency

of pleomorphic adenoma ranges from 40.9% to 73.8% of all STGs (Table 4).^{11,21} Studies involving large series of SGTs report similar results, with pleomorphic adenoma representing 60% to 73% of parotid gland tumors as well as 40% to 60% of submandibular and minor salivary gland tumors.^{11,21} All cases of pleomorphic adenoma reported in the present study were treated by surgery and recurrence was observed in four cases (3.66%).

Adenoid cystic carcinoma was the most prevalent malignant SGT (14 cases), representing 12.8% of all tumors and 58.3% of malignant tumors, followed by mucoepidermoid carcinoma and acinic cell carcinoma. The predominance of adenoid cystic carcinoma has been described in studies conducted in Congo, Tanzania, Croatia and Nigeria. In contrast, studies conducted in Iran, Brazil, Jordan, the USA, the United Kingdom and Italy report a greater frequency of mucoepidermoid carcinoma than adenoid cystic carcinoma, whereas similar distribution between these two types of SGTs has been reported in China, Finland and Mexico (Table 4). These findings

suggest geographic variation in the frequency of malignant SGTs.

Adenoid cystic carcinoma exhibited the worst behavior among all SGTs analyzed. This tumor has a slow growth pattern with the early nerve and lymph node involvement. Advanced tumors require surgery and radiation therapy.²⁵ In the present study, adenoid cystic carcinoma recurred in four cases (28.6%) and death occurred in an additional two cases (14.28%). The patients in these cases were in TNM stages III or IV and received surgery plus radiation therapy. According to previous studies, the majority of patients with distant metastasis of an adenoid cystic carcinoma have tumor size of T3 or T4 and that surgery and radiation therapy achieve excellent results regarding both local and regional control.^{5,26,27} Another important aspect is the presence of perineural invasion, which is a common finding in adenoid cystic carcinoma that appears to contribute to a worse outcome.²⁷ The mean follow-up period in the present study was 7.4 years and a high survival was observed. However, previous studies indicate that survival rates are usually high in the first five years, whereas the cure rate over a 20-year period is much lower.^{5,8,26,27}

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Conclusion

In this retrospective study, major salivary glands were more affected than minor glands by neoplastic processes and pleomorphic adenoma and adenoid cystic carcinoma were the most frequent benign and malignant tumors, respectively, at a tertiary health center in southern Brazil. Analyzing the present findings in light of data from previous studies on SGTs, one may infer that some demographic characteristics (*e.g.*, gender and age) and the predominance of malignant tumors (*e.g.*, adenoid cystic carcinoma and mucoepidermoid carcinoma) vary in different geographic regions. Factors that influence SGT behavior and prognosis should be investigated further.

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